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FOREWORD

" Australasian Annals of Medicine " has been established as the official organ of The Royal Australasian College of Physicians and is to be published in May and November of each year.

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This journal is intended to cover a wide field. It will not be restricted to the work of members of the College, but is designed as a medium for the presentation of original work carried out and investigations made in medicine and the medical sciences in Australia and New Zealand.

A. Holmes à Court,
President.

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AUSTRALASIAN ANNALS OF MEDICINE

VOLUME I MAY 1952 NUMBER 1

THE CHEMOPROPHYLAXIS AND CHEMOTHERAPY OF MALARIA IN MAN WITH SPECIAL REFERENCE TO THE LIFE CYCLE[1]

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THIS lecture commemorates a distinguished Australian health worker and scholar, Frank McCallum, who died in 1946, soon after he assumed the position of Director-General of Health for the Commonwealth. McCallum was uniquely qualified, by training, experience and rare personal attributes, for the high position he occupied for such a tragically brief period. His death must be regarded as a grievous loss to the nation, as it was to his many friends.

Frank McCallum was born at Ararat, Victoria, in 1890, and was a graduate of the Melbourne Medical School. His post-graduate education was planned with characteristic foresight and care to equip him for his life-work as a public health administrator. After strenuous war service in Gallipoli and France with the First Australian Imperial Force, he studied public health at the University of Melbourne, tropical medicine and statistics at the London School of Hygiene and Tropical Medicine, epidemiology at Johns Hopkins University, and public administration at the University of Sydney. He remained a student to the end of his days, and was endowed with a breadth of scholarship which is rare in our crowded times.

As a senior officer of the Commonwealth Health Department, McCallum achieved an authoritative position in international health affairs, including quarantine, epidemiology, nutrition and the special problems of the Pacific Region. For many years he represented the Commonwealth in London, and at the Health Organisation of the League of Nations. Alone, or in collaboration, he made considerable contributions on the epidemiology of disease in Australia. The subjects of his writings included international hygiene, the epidemiology of smallpox, intestinal infections in Australia, and the history of smallpox in this country. He was a leader of public health throughout the Commonwealth, and in the estimate of one perhaps best qualified to judge there was " no other person in Australia with the same comprehensive experience, or full knowledge of the problems to be faced in the near future ".

Through his wide interests and activities, McCallum's fine personal characters were known and appreciated throughout Australia. He had " a wide and understanding tolerance, a keen sense of humour, and an unaffected love for his fellow man "; a high sense of public service was inherent in his professional life.

As Lecturer in International Health, Frank McCallum was a valued member of the teaching staff of the School of Public Health and Tropical Medicine. He constantly encouraged its activities. To the many benefactions of his working days were added, upon his death, the bequest of his library. He is remembered with respect and affection.

Since the beginning of the present century the life cycle of the malaria parasite, with a schizogonous cycle in the red blood corpuscle of man giving rise to clinical attacks and a sporogonous cycle in the mosquito, appeared to be finally settled. Grassi (1900) had considered there might be another developmental stage in man during the incubation period, but

[1] The McCallum Memorial Lecture delivered at the School of Public Health and Tropical Medicine, University of Sydney, on November 21, 1951.

after Schaudinn (1902) published his paper with drawings giving details of just how the sporozoites penetrated the red cells, the chain of events in the life cycle appeared complete.

I. Indirect and Direct Evidence of Tissue Stages in the Malaria Life Cycle

Sergent and Sergent (1922) noted that though quinine destroyed malaria parasites after they appeared in the blood, it exerted no such effect during the incubation period. Yorke and Macfie (1924) reported that in trophozoite-induced vivax malaria transmitted by blood inoculation, radical cure could be obtained when quinine was given during the incubation period, whereas it merely prolonged the incubation period slightly in sporozoite-induced malaria acquired from infective mosquitoes.

In January 1931, James (1931*a*) read a paper at the Royal Society of Tropical Medicine and Hygiene confirming these observations, but he still considered that Schaudinn's account of the penetration of the corpuscle by the sporozoite was " so clear cut and detailed as to admit no question ". In the discussion which followed, Warrington Yorke (1931) was frankly sceptical, stating that he had spent many weeks trying to confirm Schaudinn's observations without success.

In August of the same year, James, Nicol and Shute (1931*b*) reported the prevention of mosquito-transmitted vivax malaria in experimentally infected volunteers by the use of " Plasmoquine " ; 20 milligrammes were given on the day before exposure to infection and 60 milligrammes for the following six days. James (1931*c*) considered these findings favoured the view that there was a tissue stage, and, in a paper read by Schüffner at Amsterdam in December, suggested the time had come " to consider whether knowledge concerning the life cycle of the malaria parasite was complete or not ". It is interesting to note that the following year the volunteers in James's experiment all developed vivax malaria, so what " Plasmoquine " had done was merely to delay the overt attack, and not prevent the infection as had been suggested.

(1) avian malaria

The hypothesis that there might be a tissue phase in human malaria soon received support from the discoveries made in bird malaria in which James and his colleagues played an important part. James and Tate (1937, 1938) independently described the schizogonous cycle in the reticulo-endothelial cells and monocytes of fowls infected with *Plasmodium gallinaceum*, and suggested the non-committal title " exo-erythrocytic " be used to differentiate it from erythrocytic schizogony. In this work they observed the late tissue stage of the parasite. The early tissue stage, now generally referred to as " pre-erythrocytic ", was discovered independently in *P. gallinaceum* by Müdrow (1940) and Shortt, Menon and Iyer (1940).

(2) mammalian malaria

Efforts to discover the tissue phase of the malaria parasite in man were made during the war, especially in Britain and the United States, and intensified thereafter. It was at this critical stage that the subinoculation experiments by the Land Headquarters Medical Research Unit shed an important light. The results obtained showed beyond any reasonable doubt that there was both an early and late tissue phase in vivax malaria, and an early but not a late tissue phase in falciparum malaria (Fairley *et alii* 1945, 1947). These experiments revealed that after infected mosquitoes had bitten donor-volunteers, sporozoites could be demonstrated in the circulating blood of the donor up to one hour after biting ceased, provided massive injections of 500 millilitres of blood were given intravenously into non-immune recipients. Subinoculations then became negative, and remained so for six days in *P. falciparum* infections and for eight days in *P. vivax*. Then subinoculations invariably became positive ; some one to three days later parasites were demonstrable microscopically in thick blood smears and overt primary malaria developed. This clearly indicated there was an early tissue stage of development outside the circulating blood during the incubation period in both vivax and falciparum malaria.

Following specific drug therapy in falciparum malaria, once a negative subinoculation had been established it remained negative and overt malaria failed to appear ; in other words, radical cure was achieved.

After effective treatment of the primary attack in vivax malaria, however, subinoculations which had been consistently negative for many weeks would suddenly become positive, parasites would appear in the blood films and overt attacks develop. Somewhat similar results were obtained from subinoculation in volunteers taking suppressive " Atebrin ", only here overt attacks were observed only after cessation of the suppressive drug. These observations constituted strong presumptive evidence of the existence of a late tissue phase (exo-erythrocytic schizogony) in vivax malaria.

Shortt and Garnham (1948) demonstrated that both pre-erythrocytic and exo-erythrocytic schizogony occurred in the liver of monkeys infected with *P. cynomolgi*. Later, in association with Covell and Shute (1948), they found that in man a similar pre-erythrocytic stage occurs in the liver in *P. vivax*. Indirect evidence entirely favours the view that exo-erythrocytic schizogony is established and persists in *P. vivax* as it does in *P. cynomolgi* infection, though it has not yet been demonstrated. On the other hand, in malignant tertian malaria, no difference exists in the behaviour of trophozoite- and sporozoite-induced malaria to schizonticidal drugs—either type of experimentally induced infection responding in the same way to therapy. The results of subinoculation experiments in human volunteers at Cairns indicated that there was an early but not a late tissue stage, and this early or pre-erythrocytic stage of *P. falciparum* has recently been demonstrated at the Hospital for Tropical Diseases, London, in the liver of a human volunteer, after he received 718 infective mosquito bites (Shortt *et alii*, 1949, 1951). The earliest times pre-erythrocytic forms have been found in the liver to date are three to four days in *P. cynomolgi*, four days in *P. falciparum*, and six days in *P. vivax*.

The success attained by Shortt and his colleagues, where so many others had failed, was no doubt mainly dependent on the intense hyperinfection adopted, and the improved technique devised for staining tissue parasites.

II. Anti-malarial Drugs

(1) Introductory remarks

By 1939 we knew much about quinine, a good deal about "Plasmoquine" (pamaquin) and a limited amount about "Atebrin" (mepacrine), while the Germans, who had synthesized and patented "Resochin" (chloroquine) and "Sontochin", were just beginning to investigate these drugs biologically for anti-malarial properties.

During the war the synthesis and investigation of new anti-malarial drugs in Britain and the United States of America proceeded on a gigantic scale. In connexion with the discovery of proguanil ("Paludrine") by Curd, Davey and Rose (1945) over 1000 new compounds were produced and tested against bird malaria. In the United States of America more than 14,000 new compounds were screened for their therapeutic action in bird malaria and over 100 of these were subsequently tested in man (Wiselogle, 1946). The more promising of these drugs were sent to the Land Headquarters Medical Research Unit, Cairns, for testing for suppressive and chemoprophylactic action on experimentally infected volunteers under tropical conditions.

Since the war, British work has largely been directed to studies and field trials of "Paludrine" and the experimental production of resistant strains to this drug. Workers in the United States of America have concentrated largely on the synthesis, pharmacology and clinical and experimental chemotherapeutic trials of the 4-amino-quinoline and 8-amino-quinoline compounds.

The more important anti-malaria drugs acting on the different phases of the malaria parasite now include: (1) the cinchona alkaloids (totaquine and quinine), (2) the 5-amino-acridines ("Atebrin"), (3) the 4-amino-quinolines (chloroquine and "Camoquin"), (4) the 8-amino-quinolines (pamaquin, pentaquine, isopentaquine and primaquine), and (5) the biguanides ("Paludrine").

(2) Pharmacological considerations

As the asexual parasites which are responsible for clinical symptoms undergo schizogony within the red blood corpuscles, any schizonticidal drug to be effective must be able to enter these cells in adequate concentration. With quinine the concentration attained may be only one-eighth that of the plasma (Taggart *et alii*, 1948). With mepacrine, chloroquine and proguanil the concentration in the corpuscles either equals that of the plasma or may considerably exceed it. Several factors besides permeability determine the concentration of a given drug within the corpuscle: these include the rate of its absorption from the gastro-intestine, the competition for the drug between the corpuscles and various body constituents such as the plasma proteins and tissue cells and the rate at which the body excretes and degrades it.

Mepacrine, chloroquine and "Sontochin", which are all rapidly absorbed, soon become localized in the tissues; as they are only slowly degraded and excreted, they persist in the body for long periods. The competition for such drugs between the tissue cells and corpuscles makes it necessary to give a "loading dose" if therapeutic concentrations are to be attained within the red cells. Furthermore, as reduction in the intracorpuscular concentration of these drugs is slow, therapeutic concentrations can be maintained by a low maintenance dose. These were the principles on which Shannon *et alii* (1944) based their therapeutic regime for mepacrine, and they hold equally for the

4-amino-quinolines such as chloroquine and "Sontochin" (Schmidt, 1946; Berliner *et alii*, 1948).

Proguanil is active in very low concentrations and attains a good plasma and red cell concentration, so that although it is localized in the tissues for some time there is not the same need for a loading dose (Spinks, 1946; Maegraith *et alii*, 1946).

The plasma concentrations of quinine and the 8-amino-quinolines fall very rapidly, largely as a result of degradation; consequently with these drugs frequent high doses are required and not loading and maintenance doses. In the case of the 8-amino-quinoline derivatives the plasma levels obtained are much increased by the simultaneous administration of mepacrine and proguanil, but not by quinine (Zubrod *et alii*, 1948; Jones *et alii*, 1948). However, neither of these drugs appears to enhance the action of pamaquin or other 8-amino-quinolines in the radical cure of primary vivax malaria in the way quinine does.

It has been appreciated for some time by clinicians that the blood concentration of an anti-malaria drug is not necessarily the whole story. It is now known that pamaquin itself is not the active anti-malaria agent in the radical cure of vivax malaria (Josephson *et alii*, 1950; Drake and Pratt, 1951), and there is evidence that proguanil is changed in the body into some more active substance (Hawking and Perry, 1948). As both of these drugs exert a direct action on the tissue stages of the malaria parasite in the liver, it is a fair assumption that the active agent must gain access to the infected hepatic cell for this purpose. On the other hand, chloroquine, which is an excellent schizonticide and is selectively absorbed by the liver, where it attains great local concentration, exerts no action whatever on the tissue stage of the parasite.

(3) FACTORS MODIFYING THE THERAPEUTIC RESPONSE

The asexual erythrocytic parasites are directly responsible for the clinical manifestations of malaria in man, and it is not surprising that the course of drug treatment necessary varies within considerable limits in non-immunes and those who have developed premunition or partial immunity. The factors which may modify the results obtained by specific therapy include the species of malaria parasite, the variety or strain of the particular plasmodium implicated, the presence or absence of partial immunity in the human host, racial considerations and the presence of intercurrent disease, nutritional deficiency or malnutrition.

(*a*) *Different Strains of Parasite*

Differences in strains of parasites of the same species do undoubtedly exist and may sometimes, but by no means always, account for the different therapeutic results reported from different countries. James *et alii* (1932) first demonstrated that his Rome strain of *P. falciparum* required eight times as much quinine for its therapeutic control as an Indian strain of the same species. Similarly, the Costa strain of *P. falciparum* proved more refractory than the McClendon strain (Earle, Berliner *et alii*, 1948). Covell *et alii* (1949) found that a West African strain of *P. falciparum* was more refractory to the schizonticidal action of proguanil than the New Guinea strain of the same species studied at Cairns by Fairley *et alii* (1946); no difference, however, was noted in its action as a causal prophylactic.

In *P. vivax* infections the Chesson strain was more refractory to quinine than the McCoy strain (Shannon *et alii*, 1948), while the New Guinea strain investigated in experimentally infected volunteers at Cairns in 1943 failed to be suppressed by 10 grains of quinine sulphate daily (Fairley *et alii*, 1945).

(*b*) *Malaria Premunition*

In malaria the immunity response appears to be directed essentially against the asexual erythrocytic parasites, whereas the pre-erythrocytic and exo-erythrocytic parasites located within the liver cells apparently enjoy complete protection from the cellulo-humoral immunity response.

Vivax Malaria.—This was well illustrated in the experiment demonstrating the pre-erythrocytic schizogony in vivax malaria by Shortt and his colleagues (1948). The volunteer was a general paralytic who had been experimentally infected previously with vivax malaria for therapeutic purposes. Though pre-erythrocytic forms were demonstrated in the liver of this patient, he never developed overt vivax malaria following hyperinfection nor were asexual parasites demonstrable in thick blood smears. Premunity had been established as a result of previous infection with the same strain of *P. vivax*; the immunization mechanism effectively dealt with parasitæmia and prevented overt malaria developing.

Blackburn (1948) was able to show that untreated army volunteers experimentally infected by bites from New Guinea strains of *P. vivax* developed solid tolerance and anti-parasitic immunity to their infection after prolonged primary fever associated with splenomegaly and anæmia. They developed a state of tolerance in which vivax trophozoites appeared in the peripheral blood from time to time in a density rarely exceeding one per cubic millimetre over several months of observation. Gametocytes were never seen during the period and mosquitoes fed on these subjects failed to become infected. At this stage the low densities of trophozoites caused no constitutional disturbances whatsoever; ultimately, the infected volunteers became perfectly fit, red cell counts and hæmoglobin values returned to normal and splenomegaly disappeared. Attempts to induce relapse by superinfection with the same strain of *P. vivax* were unsuccessful.

Falciparum Malaria. — Experimental sporozoite-induced infection with *P. falciparum*, in members of a community subject to reinfection in hyperendemic areas, may lead to transient parasitæmia and fever, with or without recrudescences; spontaneous recovery occurs without treatment in many instances. Treatment for a few days with small doses of quinine or other anti-malaria drugs will terminate the fever, generally eradicate parasitæmia, and so produce radical cure. Some cases prove completely refractory to superinfection. If treatment were withheld, the same dosage of *falciparum* sporozoites would result in hyperinfection and death in members of a non-immune community. In hyperendemic areas premunition has to be paid for in terms of a considerable mortality in infancy and childhood and febrile attacks with anæmia, hepatomegaly and splenomegaly, but once it is acquired and provided it be maintained malaria ceases to be a menace to the individual possessing it.

(4) CHEMOTHERAPY IN RELATION TO VARIOUS STAGES IN THE LIFE CYCLE

Chemotherapy will be first considered from the standpoint of the prophylaxis and suppression of malaria in non-immunes. The subinoculation technique adopted at Cairns by Fairley and his colleagues (1945, 1947) showed that the anti-malaria drugs could be classified into two groups: (1) the causal prophylactics acting on the pre-erythrocytic cycle, and (2) the schizonticidal suppressants inhibiting and finally destroying the asexual erythrocytic parasites.

Subsequently the action of anti-malaria drugs on other phases in the life cycle of *P. falciparum* and *P. vivax* will be considered. Special attention will be directed to the asexual erythrocytic cycle in overt malaria attacks, to the exo-erythrocytic cycle in relapsing vivax malaria and to the sexual cycle, that is, gametocytes in the peripheral blood as well as in the stomach of the mosquito. As there is no known drug which exerts a definite lethal or inhibiting action on the sporozoite, this calls for no further consideration.

(*a*) *Drugs Acting on the Pre-Erythrocytic Cycle*

Drugs having a direct action on the pre-erythrocytic cycle belong either to the biguanides or the 8-amino-quinoline series. Work on experimentally infected volunteers indicates that in falciparum malaria "Paludrine" is a true causal prophylactic destroying the pre-erythrocytic parasites in the liver and so preventing the appearance of asexual parasites in the blood (Fairley *et alii*, 1946). In vivax malaria it acts as a partial causal prophylactic inhibiting the pre-erythrocytic cycle which results both in prolonging the time before asexual parasites appear in the blood and in delaying the onset of overt malaria (Fairley *et alii*, 1946). Unfortunately to obtain a similar result with pamaquin and other 8-amino-quinolines these drugs have to be given in a dosage which is too toxic for routine use except possibly in the case of primaquine (Edgcomb, Jeffery *et alii*, 1950).

(*b*) *Drugs Acting on Asexual Parasites in the Blood*

(i) *Schizonticides as Suppressants of Malaria.*— The suppressant and possible curative action of drugs like quinine, "Atebrin" and chloroquine is dependent on their being present in sufficient concentration in the blood at the time merozoites are escaping into the circulation following rupture of the pre-erythrocytic schizonts in the liver.

Though parasites may never be demonstrable even in thick blood films during the period of daily administration of these drugs, subinoculations of 200 millilitres of blood collected from infected volunteers on the seventh day in malignant tertian malaria and the ninth day in benign tertian malaria invariably produce overt malaria in non-immune recipients, showing

that suppression is being achieved by schizonticidal action and not by direct effects on the pre-erythrocytic parasites.

Quinine.—The great drawback to quinine as a suppressive drug is that in a dosage of even 10 grains daily it often fails to produce radical cure of malignant tertian malaria and leads to a chronic latent or recrudescing infection in the presence of which blackwater fever is apt to develop. For this reason, if for no other, quinine is not the ideal suppressive drug and its use by Europeans should be discontinued.

Sulphonamides. — Sulphadiazine, sulphamerazine and sulphamezathine have all proved ineffective suppressants of both trophozoite and sporozoite induced vivax malaria in a dosage of 1·0 gramme daily. In falciparum malaria they have generally proved effective suppressants in this dosage and produced a high proportion of radical cures.

Mepacrine.—The chemotherapeutic control of malaria by mepacrine was achieved by allied troops in the Pacific and South-East Asia commands during the later phases of the second world war. Early in 1943, military volunteers were experimentally infected with New Guinea strains of malaria and it was conclusively demonstrated that in *P. falciparum* infections overt malaria failed to develop and radical cure resulted, provided the correct regime of mepacrine administration was instituted under controlled conditions prior to, during, and after exposure to infective mosquito bites. In these volunteers subinoculations, which were found to produce positive results over a period of from seven to twelve days after infective biting, soon produced negative results and overt attacks failed to appear. Volunteers infected with *P. vivax* failed to develop malaria fever when receiving mepacrine in the appropriate dosage, but they did so two to seven weeks after administration of the drug was stopped. In jungle warfare troops generally acquired mixed infections, and to reproduce field conditions experimentally it was necessary to expose volunteers repeatedly over a period of several months to large numbers of mosquitoes, some being infected with *P. falciparum*, others with *P. vivax*. During this period volunteers were subject to intense physical fatigue, severe cold, anoxia as in flying at high altitudes, and blood loss, but in no instance did overt malaria develop provided a strict mepacrine regime was followed. On an average of about thirty days after the stopping of the drug, overt benign tertian malaria appeared with great regularity, but not malignant tertian malaria.

These experiments had considerable military significance, as they indicated that troops, while under a proper mepacrine regime, could fight without significant malaria casualties in hyperendemic areas where similar strains of falciparum parasites abounded. The experiments also implied there should be no deaths from malaria, no malaria casualties and no blackwater fever, provided the daily dose of 0·1 gramme was continued for three to four weeks after malaria infected areas were left.

When the results of these experiments were reported to the military authorities, disciplinary measures in regard to mepacrine administration were widely enforced. Malaria casualties rapidly diminished in the South-West Pacific and South-East Asia commands and with few exceptions malaria ceased to be a disease of major importance to the Allies during jungle fighting (Fairley *et alii*, 1945). Later, in 1945, as well as the universal mepacrine-sensitive strains, a relatively insensitive strain of *P. falciparum* began to appear amongst some of the troops of the Sixth Australian Division located in the Aitape-Wewak area of New Guinea; this strain required 0·2 gramme daily for its suppression and larger doses than usual for therapeutic purposes. Both strains proved equally sensitive to proguanil ("Paludrine") and chloroquine (Fairley *et alii*, 1946).

Chloroquine and Related 4 - Amino - Quinolines. — Chloroquine ("Aralen") and "Sontochin" were first tested for suppressant and prophylactic action in military volunteers at Cairns during the 1943–1944 period.

The suppressive dosage used was 50 to 100 milligrammes daily of chloroquine, and 100 to 200 milligrammes of "Resochin". Results identical in all respects with those outlined for mepacrine were obtained. Malignant tertian malaria was suppressed and radically cured, while benign tertian malaria was suppressed but relapsed later. Since then chloroquine in a dosage of 0·3 gramme (base), that is two tablets once weekly, has been found to be an excellent suppressant in India, Panama, Malaya and elsewhere. "Camoquin Hydrochloride", another promising member of the group, is still under field trial. For suppressive purposes, three tablets (0·6 gramme base) are advised every two weeks. It was found by Coatney *et alii* (1950) to be an effective suppressant in volunteers experimentally infected with *P. vivax* (Chesson strain) in a single dose of 0·3 gramme (base) each week.

(ii) *Schizonticides in the Clinical and Radical Cure of Overt Malaria.*—Oral Medication.—In general it may be said that the drugs capable of acting as effective schizonticidal suppressants of malaria are also capable of producing clinical and radical cure of falciparum malaria and clinical cure of vivax and quartan malaria. The action of the cinchona alkaloids, especially of quinine in adequate dosage (20 to 30 grains daily) over a period of two to three weeks, is well-known in this respect.

Provided a large initial loading dose is prescribed, the administration of 3·0 grammes of "Atebrin" over a period of seven days results in the radical cure of falciparum malaria in most instances; for the clinical cure of benigh tertian malaria, a less intensive course suffices. Mepacrine is a somewhat more rapid and effective schizonticide than quinine administered by the oral route.

Chloroquine probably terminates the clinical attack and eliminates parasites more rapidly than any other schizonticide. Its oral administration over a three-day period (total 1·5 grammes base) is accompanied by a high radical cure rate in falciparum malaria and is stated by Coatney (1949) to be superior to a seven-day course of mepacrine (total 3·0 grammes). As with mepacrine, it is necessary to employ a large loading dose on the first day, that is 0·9 gramme (base). It does not discolour the skin and has little or no tendency to produce major toxic symptoms. Available information suggests that chloroquine given by the mouth is the most potent schizonticidal drug at present available.

"Camoquin" appears to be a very efficient schizonticide in vivax and falciparum malaria, but like the other 4-amino-quinolines it has no action on the pre-erythrocytic or exo-erythrocytic parasites in the liver or on falciparum gametocytes. The therapeutic dose advocated for adults is three to five tablets (0·2 gramme base each) taken as a single dose; for children the dosage is computed on the basis of 10 milligrammes per kilogram.

Proguanil ("Paludrine") also possesses definite schizonticidal action, and the radical cure rate has proved high with New Guinea and certain other strains of *P. falciparum*. Its action, however, in this respect is somewhat slower from a clinical viewpoint, and parasites sometimes take longer to disappear from thick blood films than with mepacrine and the 4-amino-quinolines. Therapeutic trials in Africa have yielded divergent results. In a strain of *P. falciparum* investigated by Covell and his colleagues (1949) from West Africa (Lagos) nine out of ten persons with overt primary malaria treated with 0·6 gramme of proguanil daily for ten days had recrudescences within three weeks. When proguanil was reinforced with mepacrine (0·9 gramme) on the first day, radical cure resulted. One unfortunate feature of proguanil administration is the remote possibility that resistance to it may develop. Under artificial experimental conditions a proguanil-resistant strain has been produced against *P. vivax* (Seaton and Lourie, 1949; Cooper *et alii*, 1950) and *P. falciparum* (Seaton and Adams, 1949). There is also some evidence that schizonticidal resistance may develop after long periods under field conditions (Edeson and Field, 1950; van Goor and Lodens, 1950). For this reason, when overt malaria develops in patients taking proguanil prophylactically, chloroquine and not proguanil therapy should be adopted to ensure radical cure in the acute attack.

In considering strain resistance to "Paludrine", however, it is necessary to determine whether this affects (1) asexual parasites as shown by ineffective schizonticidal action, (2) pre-erythrocytic parasites as indicated by failure of prophylactic and suppressive action to infective biting, (3) gametocytes as indicated by failure of gametocidal action in known carriers.

Actually in the naturally occurring so-called resistant strains of parasites so far studied in man, there is evidence of decreased sensitivity of the asexual parasites to the schizonticidal action of "Paludrine", but not of increased resistance of pre-erythrocytic parasites to this drug. Covell *et alii* (1949) also investigated the causal prophylactic action of proguanil in general paralytics infected with the West African strain of *P. falciparum* already referred to, which was relatively insensitive to the schizonticidal action of the drug. They found, however, even with this strain, that complete protection was afforded and malaria prevented by proguanil when given in doses of (1) 50 to 100 milligrammes daily, (2) 100 milligrammes twice a week at intervals of three to four days, or (3) 300 milligrammes once weekly.

Perhaps this is not surprising as Fairley *et alii* (1946) found that one single dose of 10 milligrammes of "Paludrine" given 48 to 120 hours after infection completely protected six out of eight volunteers from malaria, whereas a single dose of 300 milligrammes failed to prevent an overt attack when given 168 hours and 192 hours after infection, at a time when asexual parasites were present in the blood.

This suggests that pre-erythrocytic parasites are much more sensitive to " Paludrine " than asexual parasites, even with a strain like the New Guinea one, which is sensitive from a schizonticidal viewpoint.

Most of the alleged failures of " Paludrine " as a prophylactic and suppressive drug in the field appear to be due to irregular intake and inadequate dosage rather than to genuine strain resistance. In any critical investigation chemical examination of the urine for " Paludrine " should be undertaken as a routine procedure; unless this is done great care is necessary before concluding that overt malaria is due to any factor other than defective administration of the drug.

In partial immunes not taking " Paludrine " for prophylactic purposes, a single dose of 0·3 gramme of this drug generally produces clinical cure of overt attacks of benign tertian and malignant tertian malaria and would appear to be a rational procedure on economic and other grounds, provided schizonticidal-resistant strains do not develop.

Intramuscular and Intravenous Medication.—In hyperinfections with *P. falciparum* slow intravenous injections of quinine bihydrochloride (10 grains) or intramuscular injections of " Atebrin " musonate (0·36 gramme) should be given without delay and repeated in a few hours when necessary. More recently Scott (1950) has reported on the efficacy of chloroquine dihydrochloride intravenously in 110 patients with falciparum malaria, three having cerebral symptoms. Slow intravenous injections by the syringe technique produced a considerable fall in systolic blood pressure, dizziness and other symptoms, and for these reasons it was abandoned in favour of giving the standard dose of 400 milligrammes (base) in 500 millilitres of sterile saline by intravenous drip, taking one hour. With this technique no serious toxic symptoms ever developed, the temperature fell to normal within an average of 12 hours (two to 22 hours) and parasites disappeared from thick films in 46 hours (seven to 72 hours). No parasitæmia or recrudescences were observed after an average stay in hospital of seven days, but as the patients were all given an oral course of chloroquine diphosphate (1·5 gramme base) on discharge the radical cure rate could not be assessed. Scott considers a single injection of chloroquine dihydrochloride (400 milligrammes base) administered as a drip infusion to be the best method of treating patients severely ill with falciparum malaria.

(5) DRUGS ACTING ON THE EXO-ERYTHROCYTIC CYCLE IN VIVAX MALARIA

Clinical cure of mosquito-transmitted vivax malaria (sporozoite-transmitted) by any of the better known schizonticidal drugs is readily attained, as is radical cure of vivax malaria transmitted by inoculation of blood containing asexual parasites (trophozoite-transmission). Radical cure of sporozoite-transmitted malaria is, however, quite another problem, and for its solution it is necessary to employ one of the 8-amino-quinolines such as pamaquin, pentaquine, isopentaquine or primaquine in combination with quinine. All these compounds are similar to pamaquin, differing only in their terminal amino group in the aliphatic side chain in the 8-position on the quinoline nucleus (Edgcomb, Jeffery *et alii*, 1950).

Sinton and Bird (1928) first demonstrated the low relapse rate in India (8·8%) when vivax malaria was treated with quinine and " Plasmoquine " (pamaquin) some twenty-three years ago. Unfortunately, owing to the exaggerated views of the toxicity of pamaquin and the opposition of malariologists in the League of Nations, this method of treatment was largely discarded. It was revived only in the later stages of World War II. As this treatment is equally effective, whether it is given during an overt attack or in the latent period when asexual parasites are absent from the blood, the radical curative action of these drugs can be only on the late exo-erythrocytic forms in the liver. Quinine in adequate dosage not only destroys the erythrocytic asexual parasites preventing recrudescences in vivax malaria, but it exerts a synergistic action on the 8-amino-quinoline compounds or their active derivatives, enabling them to destroy exo-erythrocytic parasites more effectively, so preventing relapses.

Toxicity of 8-Amino Quinolines

Toxic manifestations include gastric-intestinal symptoms like nausea, vomiting, abdominal colic and methæmoglobincythæmia which are of little significance; rarely more severe manifestations such as hæmolytic anæmia, hæmoglobinuria and agranulocytosis appear. Both the last mentioned features call for immediate cessation of treatment. Isopentoquine is the least toxic and shows less tendency to methæmoglobincythæmia than the others. Isopentoquine can be given in a maximum of 240 milligrammes (base) daily for several weeks; with primaquine this dosage produces severe toxic symptoms within a week. The

maximum tolerated dose of pamaquin was 90 milligrammes (base) per day and that of pentaquine is 120 milligrammes, but severe damage to the nervous system may result with this dosage. The toxicity of primaquine tends to be cumulative and in some instances begins late in the course of drug administration and continues for several days after its discontinuance. The tendency to methæmoglobin formation within the corpuscle is stated to be reduced 50% when quinine is administered along with primaquine.

Therapeutic Value

Little difference in therapeutic value exists between pamaquin and pentaquine, so the latter need not be considered further.

When pamaquin, isopentaquine and primaquine are compared the chemotherapeutic index is considered to be 1 : 2½ : 10. On an equal weight basis, primaquine proved about four times as active as the best of the other members of the pamaquin group in the radical cure of vivax malaria (Chesson strain) treated during the stage of primary fever. The infections were sporozoite-transmitted by bites from ten heavily infected mosquitoes. These three drugs have been shown in field studies to be active in doses one-half to one-third as great as those necessary to produce equivalent results against the standard test strain of vivax malaria (Most *et alii*, 1946; Alving, 1948; Coggeshall and Rice, 1949).

In these experimental prison volunteers 10 out of 10 with primary vivax malaria and 20 out of 21 with relapsing vivax malaria were radically cured when 30 grains of quinine and 22·5 milligrammes of primoquine were given daily in divided doses every four hours for fourteen days. It is probable that naturally acquired infections are cured by even smaller doses of primaquine diphosphate and it is suggested that primaquine (7·5 milligrammes base) and quinine (five to 10 grains) administered at eight-hourly intervals for fourteen days would suffice (Edgcomb, Jeffery *et alii*, 1950).

(6) GAMETOCIDAL DRUGS

Though the malaria carrier is a menace to the community, especially where malaria is endemic, the treatment of carriers has generally attracted less attention than its importance merited. In hyperendemic areas of malaria, the most effective carriers are generally infants and young children, rather than older members of the community who have developed premunition or partial immunity as a result of repeated infection. Amongst non-immunes, carriers are as frequent in mature adults as in young children. Any schizonticidal drug, by terminating fever sufficiently early in the malaria attack and cutting short the trophozoite wave, may prevent or limit the development of the gametocyte wave (secondary gametocidal action). Following a bout of fever lasting a sufficient time, mature gametocytes of *P. falciparum* may appear, persisting in the circulating blood up to five or six weeks: those of *P. vivax*, however, disappear about the same time as the fever is terminated and asexual parasites are destroyed by schizonticidal drugs. Quinine inhibits the growth of very young falciparum gametocytes and growing vivax gametocytes, but not the mature forms of either species of parasite. "Atebrin" (mepacrine) affects only the growing gametocytes of *P. vivax* (Mackerras and Ercole, 1949*a*, 1949*b*). Pamaquin ("Plasmoquine") is the best known polyvalent gametocide, acting on all stages of the gametocytes of *P. falciparum* and *P. vivax*. It is probable that the other 8-amino-quinolines, that is, pentaquine, isopentaquine and primaquine, are also good polyvalent gametocides, but unfortunately they have not yet been investigated from this viewpoint. In a total dosage of 30 milligrammes (base), that is 10 milligrammes (base) thrice daily for one to two days, pamaquin renders falciparum gametocytes non-infective to mosquitoes within twenty-four hours, and causes their disappearance from the blood of carriers in three to seven days.

In Australia Mackerras and Ercole (1947) found that proguanil ("Paludrine") exerted no effect on the number or morphological appearance of falciparum or vivax gametocytes in the blood of carriers (New Guinea strains), yet in the stomach of the mosquito development never proceeded beyond the small oöcyst stage provided proguanil was present even in small quantity in the blood feed. The same effect was produced by permitting mosquitoes in the first instance to engorge partially on a normal person taking 0·1 gramme of proguanil daily, and then allowing them to complete their feed on an untreated carrier with plentiful gametocytes in the blood. Shute and Maryon (1948) confirmed these findings, using a Roumanian strain of *P. falciparum*, and suggested it was the female gametocyte on which the drug acted.

These experimental findings suggest that it would be difficult for mosquitoes, which were feeding on the blood of a population many of whom were taking prophylactic "Paludrine", to develop sporozoite infection of the salivary glands.

REFERENCES

ALVING, A. S. (1948), *Cong. Trop. Med. and Mal.*, **1**, 734.

BERLINER, R. W., *et alii* (1948), "Studies on the Chemotherapy of the Human Malarias. VI. The Physiological Disposition, Antimalarial Activity, and Toxicity of Several Derivatives of 4-Aminoquinoline", *J. Clin. Investigation*, **27**, Symposium on Malaria, *98*

BLACKBURN, C. R. B. (1948), "Observations on Development of Resistance to Vivax Malaria", *Tr. Roy. Soc. Trop. Med. and Hyg.*, **42**, 117.

COATNEY, G. R. (1949), *Bull. Pan Amer. San. Bureau*, **28**, 27.

COATNEY, G. R., *et alii* (1950), "Studies in Human Malaria; Protective and Therapeutic Trials of SN 10,751 (Camoquin) against Chesson Strain of Plasmodium Vivax", *J. Nat. Mal. Soc.*, **9**, 67.

COGGESHALL, L. T., and RICE, F. A. (1949), "Cure of Chronic Vivax Malaria with Pentaquine", *J.A.M.A.*, **139**, 437.

COOPER, W. C., *et alii* (1950), "Studies in Human Malaria; Acquired Resistance to Chlorquanide in Chesson Strain of Plasmodium Vivax", *J. Nat. Mal. Soc.*, **9**, 59.

COVELL, G., *et alii* (1949), "Studies on a West African Strain of Plasmodium Falciparum; The Efficacy of Paludrine as a Therapeutic Agent", *Tr. Roy. Soc. Trop. Med. and Hyg.*, **42**, 465.

CURD, F. H. S., DAVEY, D. G., and ROSE, F. L. (1945), "Studies on Synthetic Antimalarial Drugs; Some Biguanide Derivatives as New Types of Antimalarial Substances with both Therapeutic and Causal Prophylactic Activity", *Ann. Trop. Med.*, **39**, 208.

DRAKE, N. L., and PRATT, Y. T. (1951), "Quinolinequinones. I. Quinone and Hydroquinone Related to Pentaquine", *J. Amer. Chem. Soc.*, **73**, 644.

EARLE, D. P., BERLINER, R. W., *et alii* (1948), "Studies on the Chemotherapy of the Human Malarias. X. The Suppressive Antimalarial Effect of Paludrine", *J. Clin. Investigation*, **27**, Symposium on Malaria, *130*.

EDESON, J. F. B., and FIELD, J. W. (1950), "Proguanil-Resistant Falciparum Malaria in Malaya", *Brit. M.J.*, **1**, 147.

EDGCOMB, J. H., JEFFERY, G. M., *et alii* (1950), "Primaquine, SN 13272, A New Curative Agent in Vivax Malaria", *J. Nat. Mal. Soc.*, **9**, 285.

FAIRLEY, N. H., *et alii* (1945), "Chemotherapeutic Suppression and Prophylaxis in Malaria; Experimental Investigation Undertaken by Medical Research Teams in Australia", *Tr. Roy. Soc. Trop. Med. and Hyg.*, **38**, 311.

FAIRLEY, N. H. (1946), "Researches on Paludrine (M.4888) in Malaria; Experimental Investigation Undertaken by L.H.Q. Medical Research Unit (A.I.F.), Cairns, Australia", *ibidem*, **40**, 105.

FAIRLEY, N. H. (1947), "Sidelights on Malaria in Man Obtained by Subinoculation Experiments", *ibidem*, **40**, 621.

GRASSI, B. (1900), *R.C. Acad. Lincei*, **3**, 289.

HAWKING, F., and PERRY, W. L. M. (1948), "Activation of Paludrine", *Brit. J. Pharm. and Chem.*, **3**, 320.

JAMES, S. P. (1931*a*), "Some General Results of Study of Induced Malaria in England", *Tr. Roy. Soc. Trop. Med. and Hyg.*, **24**, 477.

JAMES, S. P., *et alii* (1931*b*), "On Prevention of Malaria with Plasmoquine", *Lancet*, **2**, 341.

JAMES, S. P. (1931*c*), "The Use of Plasmoquine in the Prevention of Malarial Infections", *Proc. R. Acad. Sci. Amst.*, **34**, 1424.

JAMES, S. P., *et alii* (1932), "Discussion: Synthetic Antimalarial Remedies and Quinine", *Tr. Roy. Soc. Trop. Med. and Hyg.*, **26**, 105.

JAMES, S. P., and TATE, P. (1937), "New Knowledge of Life Cycle of Malaria Parasites", *Nature*, **139**, 545.

JAMES, S. P. (1938), "Exo-Erythrocytic Schizogony in Plasmodium Gallinaceum Brumpt, 1935", *Parasitology*, **30**, 128.

JONES, R., *et alii* (1948), "A Study of the Prophylactic Effectiveness of Several 8-Aminoquinolines in Sporozoite-Induced *Vivax* Malaria (Chesson Strain), *J. Clin. Investigation*, **27**, Symposium on Malaria, *6*.

JOSEPHSON, E. S., *et alii* (1950), *118th Meeting of Amer. Chem. Soc. Abs. 100.*

MOST, H., *et alii* (1946), "Chloroquine for Treatment of Acute Attacks of Vivax Malaria, *J.A.M.A.*, **131**, 963.

MACKERRAS, M. J., and ERCOLE, Q. N. (1947), "Observations on Action of Paludrine on Malarial Parasites", *Tr. Roy. Soc. Trop. Med. and Hyg.*, **42**, 365.

MACKERRAS, M. J. (1949*a*), "Some Observations on the Action of Quinine, Atebrin, and Plasmoquine on Plasmodium Vivax", *ibidem*, **42**, 443.

MACKERRAS, M. J. (1949*b*), "Observations on the Action of Quinine, Atebrin and Plasmoquine on the Gametocytes of Plasmodium Falciparum", *ibidem*, **42**, 455.

MAEGRAITH, B. G., *et alii* (1946), "Absorption and Excretion of Paludrine in Human Subject", *Ann. Trop. Med.*, **40**, 493.

MÜDROW, L. (1940), "*Klinische und parasitologische Befunde und chemotherapeutische Ergebnisse bei der Hühnermalaria*", *Arch. f. Schiffs- u. Tropen-Hyg.*, **44**, 257.

SCHAUDINN, F. (1902), "*Studien über krankheitserregende Protozoen.* II. *Plasmodium Vivax, Der Erreger des Tertian Fiebers beim Menschen*", *Arb. Gesundh. Amt.*, **19**, 169.

SCHMIDT, L. H. (1946), "Pharmacology of the 4-aminoquinolines", in "A Survey of Antimalarial Drugs 1941-1945", Edited by F. Wiselogle, Ann Arbor, **1**, 94.

SCOTT, V. (1950), "Single Intravenous Injections of Chloroquine in the Treatment of Falciparum Malaria; Toxic and Immediate Therapeutic Effects in 110 Cases", *Am. J. Trop. Med.*, **30**, 503.

SEATON, D. R., and LOURIE (1949), "Acquired Resistance to Proguanil (Paludrine) in Plasmodium Vivax", *Lancet*, **1**, 394.

SEATON, D. R., and ADAMS, A. R. D. (1949), "Acquired Resistance to Proguanil in Plasmodium Falciparum", *ibidem*, **2**, 323.

SERGENT, ET., and SERGENT, ED. (1922), *Arch. Inst. Pasteur de l'Afrique du nord*, **2**, 320.

SHANNON, J. A., *et alii* (1944), "Pharmacological Basis for Rational Use of Atabrine in Treatment of Malaria", *J. Pharmacol and Exper. Therap.*, **81**, 307.

SHANNON, J. A. (1948), "Studies on the Chemotherapy of the Human Malarias. I. Method for the Quantitative Assay of Suppressive Antimalarial Action in Vivax Malaria", *J. Clin. Investigation*, **27**, Symposium on Malaria, *66*.

SHORTT, H. E., MENON, K. P., and IYER, P. V. S. (1940), " Form of Plasmodium Gallinaceum Present in Incubation Period of the Infection ", *Indian J.M. Research*, **28**, 273.

SHORTT, H. E., and GARNHAM, P. C. C. (1948), " Exerythrocytic Parasites of Plasmodium Cynomolgi ", *Tr. Roy. Soc. Trop. Med. and Hyg.*, **41**, 705.

SHORTT, H. E., COVELL, G., and SHUTE, P. G. (1948), " Pre-erythrocytic Stage of Human Malaria, Plasmodium Vivax ", *Brit. M.J.*, **1**, 547.

SHORTT, H. E., FAIRLEY, N. H., COVELL, G., SHUTE, P. G., and GARNHAM, P. C. C. (1949), " The Pre-erythrocytic Stage of Plasmodium Falciparum ", *Brit. M.J.*, **2**, 1006.

SHORTT, H. E. (1951), *ibidem*, *Tr. Roy. Soc. Trop. Med. and Hyg.*, **33**, 405.

SHUTE, P. G., and MARYON, M. (1948), " Gametocytocidal Action of Paludrine upon Infections of Plasmodium Falciparum ", *Parasitology*, **38**, 264.

SINTON, J. A., and BIRD, W. (1928), " Studies in Malaria, with Special Reference to Treatment; Plasmoquine in Treatment of Malaria ", *Indian J.M. Research*, **16**, 159.

SPINKS, A. (1946), " The Pharmacology of Paludrine in Animals ", *Tr. Roy. Soc. Trop. Med. and Hyg.*, **40**, 3.

TAGGART, J. V., *et alii* (1948), " Studies on the Chemotherapy of the Human Malarias. III. The Physiological Disposition and Antimalarial Activity of the Cinchona Alkaloids ", *J. Clin. Investigation*, **27**, Symposium on Malaria, *80*.

VAN GOOR, W. TH., and LODENS, J. G. (1950), " Clinical Malaria Prophylaxis with Proguanil ", *Documenta Neerlandica et Indon de Morbis Tropicas*, **2**, 62.

WISELOGLE, F. Y. (1946), " A Survey of Antimalarial Drugs 1941-1945 " (edited by Wiselogle), Ann Arbor, Michigan.

YORKE, W., and MACFIE, J. W. S. (1924), " Certain Observations on Malaria made during Treatment of General Paralysis ", *Tr. Roy. Soc. Trop. Med. and Hyg.*, **18**, 13.

YORKE, W. (1931), *ibidem*, **24**, 526.

ZUBROD, C. G., KENNEDY, T. J., and SHANNON, J. A. (1948), " Studies on Chemotherapy of the Human Malarias. VIII. The Physiological Disposition of Pamaquine ", *J. Clin. Investigation*, **27**, Symposium on Malaria, *114*.

THE HÆMODYNAMICS OF SUBINTIMAL HÆMORRHAGE

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> Whenever he (Anaxagoras) can, he gives a mechanical explanation.
>
> —Bertrand Russell, *The History of Western Philosophy*.

It is natural, viewing phenomena from the limited vantage-point of part of a fleeting lifetime, that we should regard our knowledge as being relatively fixed. In a profession where some degree of apparent omniscience appears to be psychologically necessary this idea is encouraged. That it is not fixed but that we are contemplating merely one point on an undulating line which shows wide ranges of knowledge and viewpoint is easily appreciated if we stand back and consider a length of this line, that is to say, some of our history.

The pendulum has swung from a mystical to a rational view and back again continuously, if irregularly, through the ages. The point of view that biological phenomena are to be explained best by way of some vital force, has held sway over long periods even until quite recently. Although the majority has preferred the mystical approach, there have always been some such as Anaxagoras, Democritus, Erasistratus, Roger Bacon, William of Occam, Francis Bacon, Descartes and an increasing number in modern times who have emphasized the importance of the scientific approach to problems. At the moment we are convinced, as much as our immediate ancestors were to the contrary, that this dependence on physical laws will bring us most surely and quickly to the truth. It is thus commonplace nowadays to appreciate the necessity of applying physical laws, as they are seen to work with inanimate objects, to biological phenomena.

Despite the prevalence of this point of view—and it is doubtful if any modern physician would deny it—there is some hesitance in the actual application of such laws to many phenomena. This is partly because a remnant of the strong attraction of the supernatural for the human mind inhibits a scientific attitude and also because the clinical art does not necessarily encourage the meticulous checking of all details of hypotheses in the manner which, sooner or later, they will demand.

The hypotheses developed to explain phenomena thus often contain components which will not bear critical examination in the light of physical laws. This is due to the two features mentioned. First, though it is uncommon these days, the authors of the hypotheses occasionally frankly prefer a vitalistic approach or else consider and state that the phenomena are inexplicable on any other basis, and secondly others merely show a lack of appreciation of the importance of physical factors and the necessity for being certain that the individual parts of the hypotheses will sustain examination from the physical viewpoint.

Thus we find, on examination of the details of an hypothesis, that a particular structure or part of an organ or tissue is thereby endowed with special powers which may seem plausible enough until they are examined closely. If we put this in terms of physics these tissues are assumed to develop energy, that is, they produce pressures, electrical potentials arise or flowing materials develop speeds which are greater than could occur in comparable circumstances in inanimate material. It is proposed here to examine a recent hypothesis which, judging by the recent literature, has become widely popularized.

This hypothesis states that an important cause of cardiac infarction is obstruction to a coronary artery by a subintimal hæmorrhage or hæmatoma which projects into the vessel and completely or partially occludes it (Nelson, 1941; Paterson, 1938; Wartman, 1938; *inter alios*). The hæmorrhage arises from small vessels in the wall and it should be apparent that the pressure developed must be greater than that in the lumen of the main vessel.

Coronary Occlusion

Cardiac infarcts, like those in other organs, are due to a sudden diminution in the supply of nutriment to the tissue. The suddenness of onset of the phenomenon as well as its serious effects on the myocardium appears to demand a gross cause in the form of a morphologically-demonstrable obstruction to the appropriate coronary vessels.

When the condition was first recognized it was considered that this obstruction must be of an obviously mechanical kind due to such as an embolus or thrombus, and this point of view was reflected in the name that was then given to the condition, namely, coronary thrombosis. As more attention was given to the post-mortem findings in this disease, it was found that there were many cases in which a gross or complete obstruction to the significant vessels could not be found. It was seen, however, that in practically all cases there was disease of the coronary arteries and some narrowing of the lumen so that gradually the term "coronary occlusion" came to be employed.

It thus became necessary to consider alterations and variations in pressure in the coronary tree, changes in the oxygen-carrying power of the blood, or of the amount of oxygen in the blood and other such morphological intangibles which, though presenting no problem to those who appreciate the importance of physiological changes, appear to have made considerable difficulties for the morphologically minded.

In the last fifteen years, since Paterson (1936) made his deductions on observations of hæmorrhages in the wall of the coronary vessels, attention has been directed more and more to the presence of these in cases of cardiac infarction. That they are present in the vessels in at least some of the cases of coronary occlusion and cardiac infarction is an easily confirmed observation (Figure I) but, presumably in response to the demand for a gross morphologically-demonstrable precipitating cause of cardiac infarction, these have come to be regarded as an important exciting cause of this condition.

At first sight this seems to be an adequate and satisfying explanation for many of the cases. The hæmorrhage may be seen in an atheromatous plaque projecting into a vessel and in such cases the lumen is greatly diminished in this region, sometimes to a slit. In some cases also there is a superadded thrombosis in the region of this hæmorrhage.

However, it is important to appreciate that the proponents of this view have exploited all the positive evidence to the full but that the negative evidence has been ignored.

PHENOMENA OF SUBINTIMAL HÆMORRHAGE

As mentioned earlier, subintimal hæmorrhages may be seen in a considerable number of the cases of cardiac infarction. The observations may be arbitrarily divided into two groups according to whether they support the hypothesis that the hæmorrhage plays a significant part in the development of the coronary obstruction or that they do not.

The positive observations are:

(i) The hæmorrhages are often present. They are found in a significant number of cases of coronary occlusion and may be found in a vessel related to the area of muscle which has undergone necrosis.

FIGURE I.
Photomicrograph of a section of a coronary vessel which shows a gross degree of occlusion so that the lumen is reduced from about a third to a quarter of the normal. There is a subintimal hæmorrhage projecting slightly into the lumen on one aspect. × 10.

(ii) The hæmatoma produced from the hæmorrhage may project into the lumen. It may be so large that the lumen may be almost or quite obstructed.

(iii) In some of these cases thrombosis occurs in the area so that the obstruction to the vessel is complete (Figure II).

As an explanation of the mode of development of a hæmorrhage in an area which is usually avascular it is noted that frequently there are capillary vessels in the atheromatous plaque (Leary, 1938). Such vessels, which may develop (on the deep aspect) from *vasa vasorum*, may be found also on the most superficial aspect of the plaque and here they may be found to

communicate with the lumen of the main artery itself. An important feature of the hypothesis, and one that is frequently emphasized, especially when it is employed in medico-legal cases to bolster up the idea that coronary occlusion is due to raised blood pressure, is that the pressure in these small vessels (that is, capillaries) is derived directly from the main vessel itself, so that it becomes sufficiently great for the vessels to rupture.

FIGURE II.
Photomicrograph of portion of a coronary artery showing a haemorrhage into the subintimal region (H) and a thrombus in the lumen (T). It is apparent that the lumen had been greatly reduced even before the hæmorrhage had occurred. × 10.

Some negative observations are:

(i) The hæmorrhages in the wall of the vessel are not necessarily found in the artery which is supplying the area of infarction. In such cases several vessels may be involved by atherosclerotic changes, and the presence of a hæmorrhage in one of them is regarded often as support for the general hypothesis without the relation of the involved vessel to the area of infarction being adequately considered from the anatomical point of view.

(ii) The hæmorrhages are sometimes found in vessels in which recent occlusion has not occurred and there need not necessarily be any new deformation of the lumen at this site. Nevertheless such examples are included in series of cases in which the interference with coronary flow is being discussed.

(iii) In some of the cases the hæmorrhages are not in the intima at all but are to be found in the media or even in the adventitia of arteries. In such cases it is clear that they could not have any significant relation to the myocardial changes.

PHYSICAL CONSIDERATIONS

Let us now consider the physical phenomena in an example of coronary occlusion where the circumstances are most favourable to the development of obstruction, that is to say, in a vessel where the hæmorrhage is in the superficial part of the atheromatous plaque.

Since the hypothesis states that the hæmorrhage from the capillary vessels is due to increased pressure within these vessels (Horn and Finklestein, 1940; Paterson, 1941) it is necessary to show that this intracapillary pressure is great enough to produce the hæmatoma. We must therefore consider two factors: the pressure within the capillaries and the extracapillary pressure in the wall of the artery.

The pressure within the capillaries is said to be high because these communicate directly with the lumen of the main vessel. The pressure within the coronary vessel is high, say, about 70 to 90 millimetres of mercury, and it is assumed that, since this is communicated directly to the capillaries, these thin-walled structures will be unable to withstand this pressure and will rupture—so producing the hæmatoma. This, however, takes no cognizance of Poiseuille's law.

Poiseuille's law states that the difference in pressure between two points in a system, in which there is a stream-line flow of a viscous fluid, is directly related to the length of tube, the viscosity of the fluid, the rate of the volume flow, and is inversely proportional to the fourth power of the radius. This may be shown by the formula

$$P=\frac{8L}{\pi R^4}\eta I$$

where P is the pressure difference, L is the length of tube between the points of pressure, R is the radius, η is the viscosity, and I is the rate of volume flow.

There are difficulties in applying this equation to actual circumstances in the human body largely because the rate of flow in the capillaries is not known precisely. In addition to this the apparent viscosity varies considerably in different vessels according to their size; in the very small vessels it may be only a third or a quarter of what it is in the larger vessels. Nevertheless, though it may not be possible to

say accurately what is happening in these tubes, it is apparent that the fall of blood pressure will be great in small vessels.

Without going into further details, it is clear that the smaller the vessel the greater the fall of pressure along a tube, so that in the tiny capillaries the pressure transmitted from the lumen of the vessel will be quickly dissipated. In any case it is assumed by the hypothesis that the capillaries are relatively easily ruptured by moderate pressures. Observations in various conditions would suggest, however, that capillaries are able to withstand relatively high pressures or, at any rate, pressures which are much higher than might be expected to be withstood by such thin-walled structures. Incidentally we are not discussing here any of the conditions causing bleeding as a result of changes in the blood or of the capillary permeability.

Another point which is seldom appreciated is that the walls of these capillaries are semipermeable membranes. Alterations of pressure within these vessels results in the rapid transfer of fluid either from within out, or *vice versa*. The result is that, following a change, there is a rapid approximation of pressures outside the vessel to those within them.

In addition to this the pressure in the main vessel itself will be transmitted to the tissue of the wall, so that there would be little discrepancy between the pressures outside and inside the capillaries. Thus the pressure within the capillary vessels in the wall cannot be greatly different from the pressure in the tissues around them for two reasons: (1) pressure from the lumen is communicated not only to the lumen of the capillaries themselves but also is transmitted to the wall of the vessel; and (2) even if there should be a discrepancy in the intracapillary and extracapillary pressures, this would be adjusted automatically by the transfer of fluid through the semipermeable membrane which is the capillary wall.

There may be, and indeed are, considerable variations at different times of the pulse wave corresponding to the changes in pressure in the different stages of the cardiac cycle and phenomena such as mural hæmorrhage may possibly occur only at one stage of these. However, when we consider separate phases in different parts of the cycle, it is apparent that these come within a limited range of pressures; thus a study of any one phase (for example, diastolic) will give some general idea of the kind of differences of pressure between that of the lumen and of small vessels in the wall.

An important point already mentioned is that, if a hæmorrhage in the wall of a vessel is to encroach on the lumen of that vessel, then the pressure in the mural hæmatoma must be greater than that in the lumen of the main vessel. This means that the pressure in the mural or subintimal capillaries must be greater than that in the lumen of the vessel. Yet such capillary pressure is, *ex hypothesi*, derived from that of the lumen!

Discussions of this kind depend on the assumption that the pressure in the main artery (at the site of capillary rupture) is actually high and of the order of pressures ordinarily seen in such vessels. However, these hæmorrhages develop in an atheromatous plaque and such a plaque usually projects into the lumen or is associated with thickening of the wall so that already there is a reduction in the size of the lumen at this site.

Here, we must consider another physical principle. Bernoulli's principle or law states that in a tube of flow for which the motion is stream-line, the total energy per unit volume is constant and is the sum of three factors, the potential energy (ρgh), the pressure energy (p) and the kinetic energy ($\frac{1}{2}\rho v^2$). In special circumstances, for example, if the flow is horizontal or if the deviation from a horizontal plane is negligible then the potential energy or gravity effect can be excluded.

Now in ideal conditions, that is in the absence of friction, since the total energy per unit volume remains constant the pressure energy and the kinetic energy are complementary.

Thus we have the formula

$$p_a+\tfrac{1}{2}\rho v_a^2=p_b+\tfrac{1}{2}\rho v_b^2$$

where p_a is the pressure at the point a in Figure III, p_b is the pressure at the point b, ρ is the density of the fluid, and v_a and v_b are the speeds of flow at the points of a and b respectively.

When fluid passes through a constriction its speed, and therefore its kinetic energy, is increased. This means that its pressure energy is diminished. If the lumen is narrowed sufficiently, the kinetic energy may be so raised that the pressure energy may be very low in this region. This phenomenon is seen and utilized in the everyday world in the water suction pump seen in the laboratory, in the Venturi tube used in gasoline carburettors and in jet engines.

When this is adapted to a case of a simple obstruction to a main branch of a coronary vessel, we can make some simple calculations.

Suppose we take an example (Figure III) in which arbitrarily

lumen at a = 3 mms. in diameter
lumen at b = half that of area at a
ρ = 1·06 g./cm.^{3}

Total coronary flow = 250 c.cms. per minute.

In the first place, speed of flow of stream at a (v_a) may be determined where

L = length of a column of blood/time
A = area of cross section of vessel
V = volume flow/time

$$L \times A = V$$

$$\therefore\ L = \frac{V}{A} = v_a.$$

If we take the flow in a first division of one coronary vessel as a quarter that of total coronary flow, this will be:

$$\frac{250}{4} \text{ c.cms. per minute} = \frac{250}{4 \times 60} \text{ c.cms. per second}$$

$$\therefore\ v_a = \frac{250}{240} \times \frac{1}{\frac{3}{10} \times \frac{3}{10} \times \frac{11}{14}}$$

$$= \frac{250}{240} \times \frac{1400}{99}$$

$$= 14{\cdot}73 \text{ cms./second.}$$

The flow at b (v_b) may be calculated:

$$\therefore\ \frac{v_b}{v_a} = \frac{\text{area } a}{\text{area } b}$$

When area a is twice that of b

$$v_b = 2v_a.$$

Now $p_a + \frac{1}{2}\rho v_a^2 = pb + \frac{1}{2}\rho v_b^2$

$$p_a - p_b = \tfrac{1}{2}\rho v_b^2 - \tfrac{1}{2}\rho v_a^2$$
$$= \tfrac{1}{2}\rho(v_b^2 - v_a^2)$$
$$= \tfrac{1}{2}\rho(4v_a^2 - v_a^2)$$
$$= \frac{3}{2}\rho(v_a^2)$$
$$= \frac{3}{2} \times 1{\cdot}06 \times (14{\cdot}73)^2$$
$$= 345 \text{ dyne cm.}^{-2}$$
$$= 3{\cdot}52 \text{ mms. } H_2O.$$

If, however, the area at b is one-third that at a

$$p_a - p_b = \frac{8}{2} \times 1{\cdot}06 \times (14{\cdot}73)^2$$
$$= 920 \text{ dyne cm.}^{-2}$$
$$= 9{\cdot}38 \text{ mms. } H_2O.$$

If area of b is one-quarter, that is if diameter at b is half that at a

$$p_a - p_b = \frac{15}{2} \times 1{\cdot}06 \times (14{\cdot}73)^2$$
$$= 1725 \text{ dyne cm.}^{-2}$$
$$= 17{\cdot}6 \text{ mms. } H_2O.$$

If the area at b is one-sixth that at b

$$p_a - p_b = \frac{35}{2} \times 1{\cdot}06 \times (14{\cdot}73)^2$$
$$= 4043 \text{ dyne cm.}^{-2}$$
$$= 41{\cdot}2 \text{ mms. } H_2O.$$

These differences are only slight, but it is clear that with progressive diminution of the lumen there is a relatively more rapid diminution of the pressure at this place.

If we consider the conditions during exercise when as much as 1500 cubic centimetres of blood passes through the coronary circulation in a minute (Lovatt Evans, 1949), the reduction in pressure is great.

Flow through the vessel

$$v_a = \frac{1500}{240} \times \frac{1}{\frac{3}{10} \times \frac{3}{10} \times \frac{11}{14}}$$

$$= \frac{1500}{240} \times \frac{1400}{99}$$

$$= 88{\cdot}38 \text{ cms. per second.}$$

If the area at b is one-half that at a

$$p_a - p_b = \frac{3}{2} \times 1{\cdot}06 \times (88{\cdot}38)^2$$
$$= 12420 \text{ dyne cm.}^{-2}$$
$$= 126 \text{ mm. } H_2O.$$

When area at b is one-third that at a

$$p_a - p_b = \frac{8}{2} \times 1{\cdot}06 \times (88{\cdot}38)^2$$
$$= 338 \text{ mm. } H_2O.$$

When area at b is one-quarter that at a, that is diameter is one-half

$$p_a - p_b = 634 \text{ mm. } H_2O.$$

When area at b is one-fifth that at a, that is diameter is four-ninths

$$p_a - p_b = 1023 \text{ mm. } H_2O.$$

Even though the pressure in the coronary vessels in these last circumstances is higher than normal, it will be seen that the pressure difference approaches the pressure at a, that is to say, the pressure at b is very low (a pressure of 110 mm. Hg equals 1496 mm. H_2O).

A considerable reduction in the pressure in the lumen must take place originally for hæmorrhage (with encroachment on to the lumen) to occur, and thus a considerable reduction in the size of the lumen is a necessary prerequisite to hæmatoma formation.

Since, with diminution of the size of the lumen, the pressure falls, it is apparent that any encroachment on the lumen will result in a still lower pressure in the lumen at the site; any pressure in the wall, therefore, will become more effective, that is to say a progressive phenomenon, going on to complete obstruction of the vessel, may arise.

The calculations given above have been made on the basis of specific and well-defined differences between the lumen of a vessel at a normal zone at the site of an obstruction and

on the assumption that, for the purposes of the calculations, these remain constant. However, it is known that when there is any diminution in the oxygen supply of the part or when the body generally or the heart is subjected to extra stress, there will be dilatation of the vessels. This of course can occur only in vessels which are resilient and are thus capable of dilatation. It will not happen where there is gross thickening of the vessels, especially when this thickening is due to atheroma.

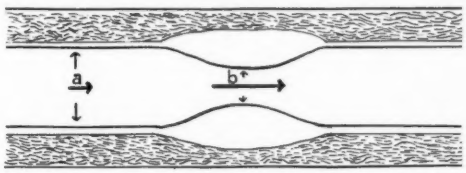

FIGURE III.

Diagram of a vessel in which there is diminution in the area of the lumen at one point (b) due to thickening of the intima. The velocity of the stream at (b) is greater than that at (a) and the lateral pressure at (b) will be less than that at (a).

In these circumstances, therefore, there will be dilatation of the normal lumen (at *a*) but not at the narrow point (*b*), and thus there will be even a greater discrepancy than previously; thus, though the measurements that have been given, and on which the calculations were made, will not necessarily remain correct for special circumstances, it will be seen that changes which are likely to occur will be in the direction of a greater difference between the two areas discussed and thus even further diminution of pressure at the constricted point.

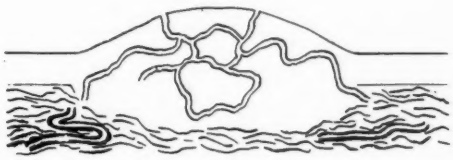

FIGURE IV.

Diagram to show capillary spaces in a thickened area of the wall of a vessel, to emphasize the very small size of these vessels in relation to the size of the lumen of the main vessel. Compare Figures V and VI.

It is thus easy to see that it is at times of increased blood flow that hæmorrhage into the wall of the vessel is likely to occur, though it is so for reasons different from those usually stated. The important point, however, is that various changes in the vessels and changes in blood flow, which are commonly seen and which cannot easily be allowed for in a mathematical equation (mainly because the information about them as yet is not sufficiently definite), nevertheless trend in a general direction which supports and augments the arguments based on relatively rigid premisses rather than acting in a contrary direction.

It has been mentioned above that the communication of capillaries in the atheromatous plaque with the lumen of the artery (Figure IV) is regarded as specially significant in the development of hæmorrhages and from this point of view it is clear that we have two sets of conditions:

(i) The pressure in the lumen of the main vessel is relatively high; thus though the capillary pressure (particularly adjacent to the lumen) may be regarded as also high, the extracapillary tension in the wall (supporting the vessels) is correspondingly high for two reasons: (*a*) because of direct transmission of pressure from the lumen into the wall, and (*b*) because of the diffusion of fluid through the semipermeable walls of the capillaries; or

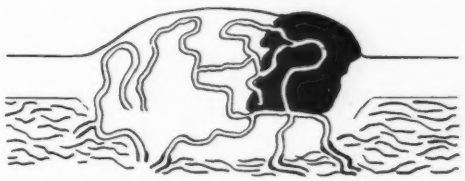

FIGURE V.

Diagram showing vascularized thickening of the wall of a vessel, these vessels communicating with the *vasa vasorum*. Provided that the pressure in the lumen of the main vessel is low, hæmorrhage could occur from these vessels.

(ii) The pressure in the lumen of the main vessel is low: even though the extracapillary tension must also therefore be low, it is apparent that the intracapillary pressure cannot be high and thus again the discrepancy between extracapillary and intracapillary tensions is not great. In either circumstance hæmorrhage is not likely to occur.

There are conditions, however, in which the capillary pressure may be significantly different from the pressure in the wall, such as when the capillaries derive their blood from the *vasa vasorum* (Figure V) or if they communicate with vessels which arise directly from the lumen of the main artery at a wider part (Figure VI).

Thus, provided that the capillaries obtain their blood from vessels which allow them to have a positive pressure in the circumstances when the pressure in the lumen of the artery is

low, it will be appreciated that hæmorrhage may possibly occur. At the same time if the blood in the capillaries is derived from the lumen where the pressure is low, then it is not possible for hæmorrhage to take place as the result of mechanical factors. When such hæmorrhage does occur it is seen that the hæmatoma encroaches on the lumen of the vessel and, unless the pressure here is already low, this is a phenomenon difficult or even impossible of explanation. If, however, the lumen is narrow and the pressure correspondingly low, then it is a readily understandable and explicable phenomenon.

At the same time, however, the blockage, which is usually part of one or associated with one which extends irregularly for some distance along the vessel wall, will cause a significant

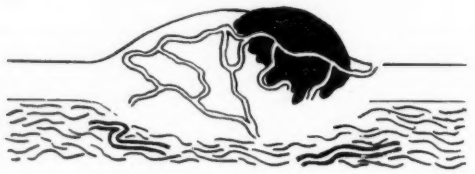

FIGURE VI.

Diagram of portion of the wall of an artery showing an area of thickening which is vascularized and the capillary vessels communicating with the lumen at a point where the lumen is of normal diameter. Since the pressure at the site of obstruction will be less than at a wider part, it is possible in this case for hæmorrhage to occur from the vessels.

reduction in flow to the distal part because of loss of energy by friction and, from the point of view of nutrition of the myocardium, such a vessel will have become relatively unimportant and the previous survival of the area will be due to, and its nutrition will be supplied by, collateral vessels.

It is not proposed here to enter into a discussion of whether the vascularized zones that are responsible for the hæmorrhages are vascularized atheromatous plaques (Leary, 1938) or organized thrombi (Duguid, 1946; Geiringer, 1951). The arguments regarding the physical factors determining hæmorrhages in these areas will apply to either circumstance.

In résumé, the most important feature, however, is that an analysis of the physical phenomena shows that hæmorrhage cannot occur (from purely physical reasons) in a vessel which is normal in size and has a normal range of pressure and that a hæmatoma cannot occlude and obstruct a normally functioning artery. On the other hand when the artery is diseased and the size of the lumen reduced, the pressure is so lowered that hæmorrhage may take place from small vessels in the wall. In such cases, however, the efficiency of the vessel as a conducting medium has been so reduced that any encroachment on the lumen by a hæmatoma will not significantly influence this further.

Much of this discussion has arisen from examination of the view that mechanical factors are the most important, if not the only ones. This is because the usual hypothesis is based on this premiss. Almost certainly, however, other factors enter into the matter in actual conditions, but beyond demonstrating that mechanical factors do not play the part usually assigned to them, it is not proposed to go in this paper.

CONCLUSIONS

Subintimal hæmorrhages are found in coronary arteries in cases of cardiac infarction and are regarded as being an important ætiological factor in some cases.

It is usually stated that such hæmorrhage arises from capillaries in atheromatous plaques and that such capillaries communicate with the lumen of the vessel. It is assumed that hæmorrhage occurs because of the high pressure in the thin-walled vessels.

If the hæmatoma is to form and project into the lumen the pressure must be greater in this region than in the lumen of the vessel. According to Poiseuille's law the pressure, provided that the capillaries derive their blood from the main vessel, must be lower than that in the lumen of the main vessel.

These capillaries are found in areas of thickening of the wall or in atheromatous plaques where the lumen is necessarily narrowed. Here, according to Bernoulli's principle, the pressure in the lumen is low and may be very low.

Hæmorrhage thus occurs because, provided the capillaries are supplied from some other vessels, pressure in them may exceed that in the lumen of the vessel.

Hæmorrhage into the media or adventitia demands the application of different principles and it is clear, from consideration of such conditions as dissecting aneurysm, that changes in the vessels and in the tissue of the wall are important.

The condition necessary for hæmorrhage to occur in the intima of an artery therefore will be found when there is already alteration in the size of the lumen and obstruction to the flow of

blood. In such cases there will have been adjustments in the circulation and development of subintimal hæmorrhage and associated thrombosis is not the exciting factor in the occlusion and cardiac infarction is shown by the frequent lack of correlation between the age of the subintimal hæmorrhage or thrombus and that of the infarct. Also their occurrence in vessels which cannot have been functionally significant as far as the area of tissue constituting a particular infarct is concerned must be considered.

The importance and interest of subintimal hæmorrhages as morphological phenomena is undoubted, but they have been given an importance and significance out of all proportion to their real status. It is necessary to look elsewhere in the physiology of the circulation for the explanation of cardiac infarction in these cases. It is not due to vascular obstruction from subintimal hæmorrhages of coronary vessels.

REFERENCES

DUGUID, J. B. (1946), " Thrombosis as a Factor in the Pathogenesis of Coronary Atherosclerosis ", *J. Path. and Bact.*, **58**, 207.

GEIRINGER, E. (1951), " Intimal Vascularisation and Atherosclerosis ", *J. Path. and Bact.*, **63**, 201.

HORN, H., and FINKELSTEIN, L. E. (1940), " Arteriosclerosis of the Coronary Arteries and the Mechanism of their Occlusion ", *Am. Heart J.*, **19**, 655.

LEARY, T. (1938), " Vascularization of Atherosclerotic Lesions ", *Am. Heart J.*, **16**, 549.

LOVATT, EVANS C. (1949), Starling's " Principles of Human Physiology ", J. and A. Churchill, London, 601.

NELSON, M. G. (1941), " Intimal Coronary Artery Hæmorrhage as a Factor in the Causation of Coronary Occlusion ", *J. Path. and Bact.*, **53**, 105.

PATERSON, J. C. (1936), " Vascularization and Hemorrhage of the Intima of Arteriosclerotic Coronary Arteries ", *Arch. Path.*, **22**, 313.

PATERSON, J. C. (1938), " Capillary Rupture with Intimal Hemorrhage as a Causative Factor in Coronary Thrombosis ", *Arch. Path.*, **25**, 474.

PATERSON, J. C. (1941), " Some Factors in the Causation of Intimal Hemorrhages and in the Precipitation of Coronary Thrombi ", *Canad. M.A.J.*, **44**, 114.

WARTMAN, W. B. (1938), " Occlusion of Coronary Arteries by Hemorrhage into their Walls ", *Am. Heart J.*, **15**, 459.

EBSTEIN'S DISEASE : A REPORT OF FIVE CASES

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Introduction

In 1866 Wilhelm Ebstein, then a young prosector at Breslau, reported the case of Joseph Prescher, a youth of nineteen who, after a short illness, died of congestive cardiac failure. He had suffered from dyspnœa and palpitation since childhood and during his last illness had shown signs of tricuspid regurgitation. At autopsy Ebstein found a congenital malformation of the tricuspid valve and right ventricle, which he rightly believed had not been described before. Up till the end of 1950 reports have appeared of twenty-seven more examples of this malformation proven at autopsy and in none of them was the correct diagnosis made during life. Indeed, it is only recently that it has been thought possible to make a correct clinical diagnosis. The present interest in this malformation derives from two facts : first, that it has been confused with pulmonary stenosis with or without over-riding aorta, and secondly, that surgical intervention in Ebstein's disease has usually been fatal.

During the past fifteen months we have encountered four patients in whom the clinical diagnosis of Ebstein's disease seemed justified. A fifth patient presented after this manuscript had been prepared and the case history is included as an appendix. In one case the diagnosis has been confirmed at autopsy while in two others the findings at cardiac catheterization or angiocardiography have supported the clinical impression. In the fourth and fifth patients the diagnosis has been made on clinical grounds alone. In view of the rarity of this disease, the clinical histories and physical findings of these cases will be given in detail and will be followed by a discussion of the clinical features and a description of the functional pathology. The latter differs in some ways from that given by previous writers.

Case Histories

Case I

A female patient, aged sixteen years, was first seen on September 21, 1950. Her mother stated that she appeared normal at birth but at three months she developed pneumonia, for which she was admitted to the Royal Alexandra Hospital for Children, Sydney. Inquiries showed that nothing abnormal was noted about her heart but unfortunately no X-ray pictures were taken. Recovery was uneventful. The patient had a second attack of pneumonia at the age of seven. She developed normally although her mother has always regarded her as backward in comparison with her other children. She attended school and had difficulty only with competitive games and physical culture classes. When she was twelve she was found to have an abnormal cardiac contour at a routine examination. Four years later she was referred to us following another routine X-ray examination of her chest. She

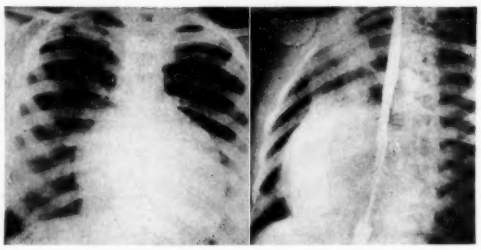

Figure Ia Figure Ib

Case I. (A) Postero-anterior and (B) left oblique view of the chest

is now working in a light job in a factory and can manage very well. She becomes short of breath on severe exertion and does not play games ; she goes dancing and stays out late. During cold weather she has been slightly blue but never persistently. She has never squatted or had syncopal attacks, and there has never been any pain in the chest or palpitation. Menarche occurred at the age of fourteen. During the twelve months she has been under our care there has been no change in her symptoms. She is the last of nine children, all of whom are taller than she is and apparently healthy. There is no history of maternal rubella.

Physical Findings. The patient was a short squat girl, four feet eleven inches high, weighing eight stone four pounds, with no clubbing of the fingers or central cyanosis but the fingers and toes were cold and slightly blue. The jugular venous pressure and wave form were normal. The pulse was of normal volume, regular in time and amplitude ; its rate was 80 per minute. The blood pressure was 130 millimetres of mercury, systolic, and 80, diastolic. The apex beat was in the fifth left intercostal space four and a half inches to the left of the mid-sternal line and was barely

palpable. A weak systolic impulse was palpable over the outflow tract of the right ventricle in the third and fourth left intercostal spaces. No thrills or pulmonary artery pulsations were present. The heart sounds were rather faint but otherwise normal. There was an inconstant grade 1 systolic murmur heard in the fourth left intercostal space at the sternal border. No third sound or diastolic murmur was heard. The femoral pulses were normal. There was no œdema or abnormality of the abdomen or lungs.

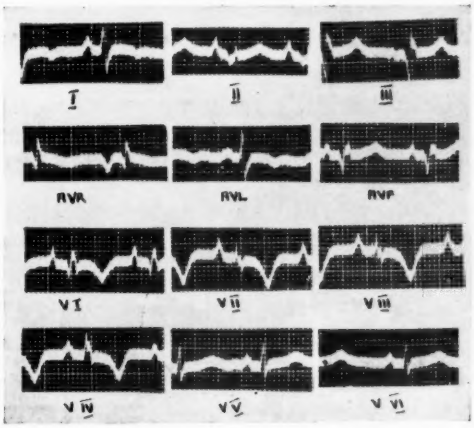

FIGURE II

Case I. Electrocardiogram showing right bundle branch block P-R int. = 0·16 second. Duration of QRS = 0·12 second

The X-ray films (Figure I) showed an increase in the transverse diameter of the heart (cardio-thoracic ratio 0·6), which was globular in shape. The right auricular convexity was increased and the infundibulum of the right ventricle was prominent. The pulmonary arteries and lung fields were normal and the aorta was left-sided. On fluoroscopy right auricular contractions

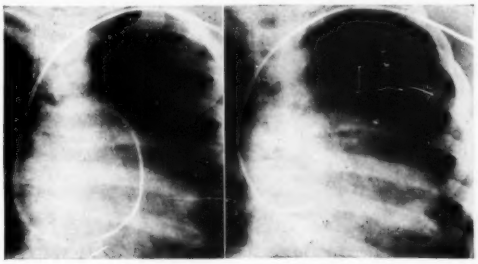

FIGURE IIIA FIGURE IIIB

Case I. (A) To show cardiac catheter in the pulmonary artery. (B) Showing catheter at the approximate site of the atrio-ventricular ring

were remarkably abrupt and of increased amplitude. In the left oblique view the right ventricle was enlarged and pulsated rather less than usual. The left ventricle was displaced backwards. The left auricle seen in the right oblique view was normal.

The electrocardiogram (Figure II) showed spiked P waves and right bundle branch block. The hæmoglobin content was 13·9 grammes *per centum*, the red blood cells numbered 4·56 million per cubic millimetre, the white blood cells numbered 10,400 per cubic millimetre with normal differential count. The erythrocyte sedimentation rate (Wintrobe) was 5·0

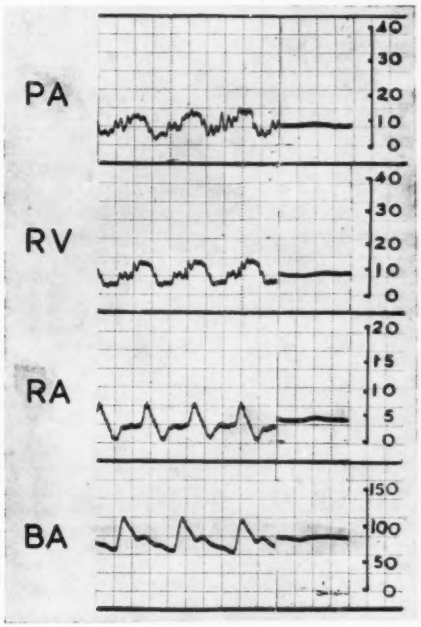

FIGURE IV

Case I. Pressure tracings not simultaneous. Note the similarity of the tracings in the pulmonary artery (P.A.) and right ventricle (R.V.) and the moderate "a" wave in the right auricular tracing. For interpretation see text

millimetres in one hour. The results of cardiac catheterization appear in Table I and the pressure tracings are illustrated in Figure IV.

Case II

A male patient, two years and seven months in age, was first seen on July 10, 1951. This child was referred because of a murmur first heard by the family doctor at the age of eighteen months. The child had been difficult to feed for the last twelve months and had not gained weight during that period. Nevertheless he was full of energy and was able to run about without any handicap. Cyanosis had never been noticed and no other relevant information was obtained from the mother, who had been well throughout her pregnancy with the child.

On examination he was a small red-cheeked child, anxious but in no distress. He weighed 26 pounds. Temperature and respiration were normal. There was no clubbing of the fingers or cyanosis. The pulse was of normal volume and regular at a rate of 120 per minute. The jugular venous pressure was difficult to determine on account of the child's restlessness, but it did not appear elevated and the wave form was normal.

TABLE I

Site.	Pressures. (Millimetres of Mercury.)			Oxygen Content. Volume Percentage.	Remarks.
	Systolic.	Diastolic.	Mean.		
Pulmonary artery	13	4	8	13·3	Film (Figure IIIA).
Right ventricle outflow tract ..	13	4	8	13·3	
Right ventricle body	13	4	8	13·3	Film (Figure IIIB).
Right auricle	7	1	4	14·0	Oxygen consumption, 97% saturated.
Brachial artery	108	58	78	18·0	
Superior *vena cava*	—	—	—	14·0	
Inferior *vena cava*	—	—	—	14·1	

Oxygen consumption = 193 cubic centimetres per minute; respiratory quotient = 0·78; arteriovenous oxygen difference = 18·0–14·0 = 4·0 volumes *per centum*; cardiac output = 4·8 litres per minute; cardiac index = 3·3 litres per square metre per minute; stroke volume = 40 cubic centimetres per stroke.

The apex beat was in the anterior axillary line and was soft and tapping in character. There were no thrills. There was a systolic pulsation in the left parasternal region felt best in the second and third left intercostal spaces. On auscultation there was a triple rhythm, the added sound occurring rather nearer the first sound than the second, but the rate was rapid and timing was difficult. The pulmonary second sound was widely split but not accentuated. There was a grade 1 systolic murmur down the left border of the sternum, maximal in the fourth left intercostal space. There was no diastolic murmur. Femoral pulses were normal. The remainder of the physical examination was within normal limits.

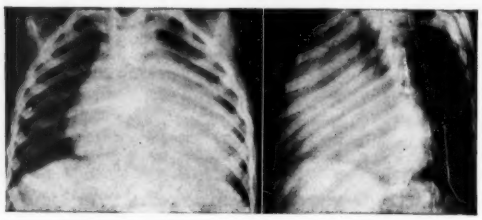

FIGURE VA FIGURE VB

Case II. (A) Postero-anterior and (B) left oblique view of the chest showing considerable cardiac enlargement due to dilatation of the right-sided chambers

X-ray examination (Figure V) showed that there was considerable cardiac enlargement (cardio-thoracic ratio 0·75). The right border was displaced to the right and was more convex than usual. The left border was displaced to the left and was extremely convex with lifting of the apex. The aortic arch was left sided and the vascular markings of the lung fields were normal. The vascular pedicle was of normal width. In the left oblique view the anterior margin of the heart was in contact with the chest wall and posteriorly the left ventricular border extended well across the vertebral bodies, resembling the cœur-en-sabot appearance. Fluoroscopy was unsatisfactory and gave no further information, except to confirm the normal appearance of the lung fields. Right auricular movements were n remarked on.

The electrocardiogram (Figure VI) showed sinus rhythm at a rate of 150 per minute, with the *P* and *T* waves superimposed. The *P* waves were tall and spiked. The *QRS* complex showed right bundle branch block was bizarre *QRS* complexes. The *PR* interval was 0·19 second, which at this rate represents first degree heart block. The hæmoglobin content was 13·0 grammes *per centum* and the red blood cells numbered 4·8 million per cubic millimetre. The white cell count was normal.

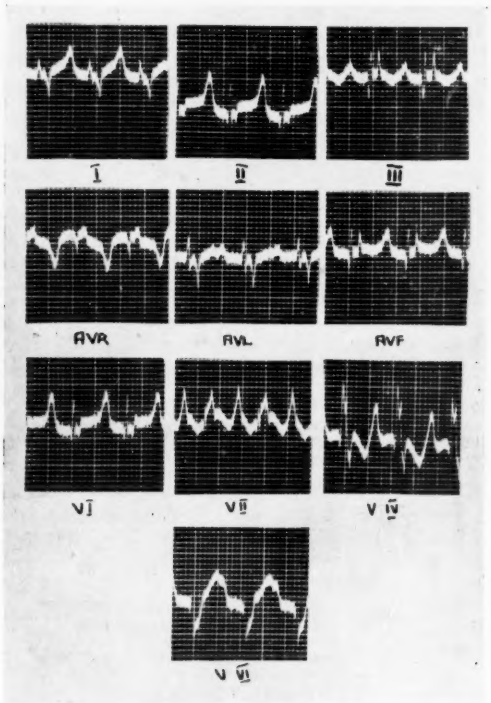

FIGURE VI

Case II. Electrocardiogram showing tachycardia, tall spiked *P* waves and right bundle branch block. *PR* interval = 0·19 second, duration of *QRS* = 0·12 second

On October 18, 1951, under basal "Avertin" anæsthesia, cardiac catheterization was begun. When the catheter reached the superior *vena cava* cardiac arrest occurred. Resuscitation was successful and the procedure was abandoned. The child was returned to the ward semi-conscious and in good condition, but died suddenly two hours later.

An autopsy was performed twenty-four hours after death. The only abnormalities were in the heart, which was described by Dr. V. J. McGovern as follows (Figure VII) :

> The heart weighs 90 grammes. The right atrium is greatly dilated and there is hypertrophy of the muscular wall both of the anterior part (*musculi pectinati*) and the posterior part. The anatomical relations of the right atrium seem normal. The *vena caval* orifices are normal, that of the inferior *vena cava* being guarded by a vestigial valve. The coronary sinus and its valve are normal. The *foramen ovale* is normally situated and measures three millimetres in diameter. It is closed by a valve which admits a probe only. It was almost certainly functionally closed. The auriculo-ventricular ring is dilated and two fingers placed in it can be passed beneath the malformed anterior cusp of the tricuspid valve to the apex of the right ventricle. The right auricular wall measures three millimetres in its posterior and thinnest part. The right ventricle and the tricuspid valve are grossly malformed ; the latter has one large leaflet and two rudimentary leaflets. The large leaflet, which would ordinarily have been the anterior leaflet, is lateral in position. This leaflet is roughly triangular in shape. Its free border is medial and extends from the infundibulo-ventricular crest at its septal attachment to the mid-zone of the right ventricle anteriorly. Its posterior and anterior borders meet laterally to form the apex of the triangle. The posterior border extends from the infundibulo-ventricular crest along the anterior border of the atrio-ventricular ring. The anterior border extends directly laterally from the mid-zone of the right ventricle. This leaflet is a thin membrane ribbed by fibrous bands which represent rudimentary *chordæ tendineæ*. There is a small hole in the leaflet near its apex. One of the rudimentary leaflets is attached to the interventricular septum beneath the infundibulo-ventricular crest. It is the size of a small finger-nail. Anterior to this cusp and merging with it at one edge there is another rudimentary leaflet attached mainly to the anterior wall of the ventricle. There is a commissure between this and the anterior attachment of the main leaflet. This second rudimentary cusp measures 15 millimetres in length and is 10 millimetres wide at its septal attachment.
>
> The free edge of the large anterior cusp measures approximately 33 millimetres and together with the septum forms the boundary of a communication between the proximal and distal parts of the right ventricle. The infundibulum is small and the pulmonary artery rises normally from it. The pulmonary valve is normal and measures 30 millimetres in circumference. The pulmonary artery is considerably smaller than normal. The

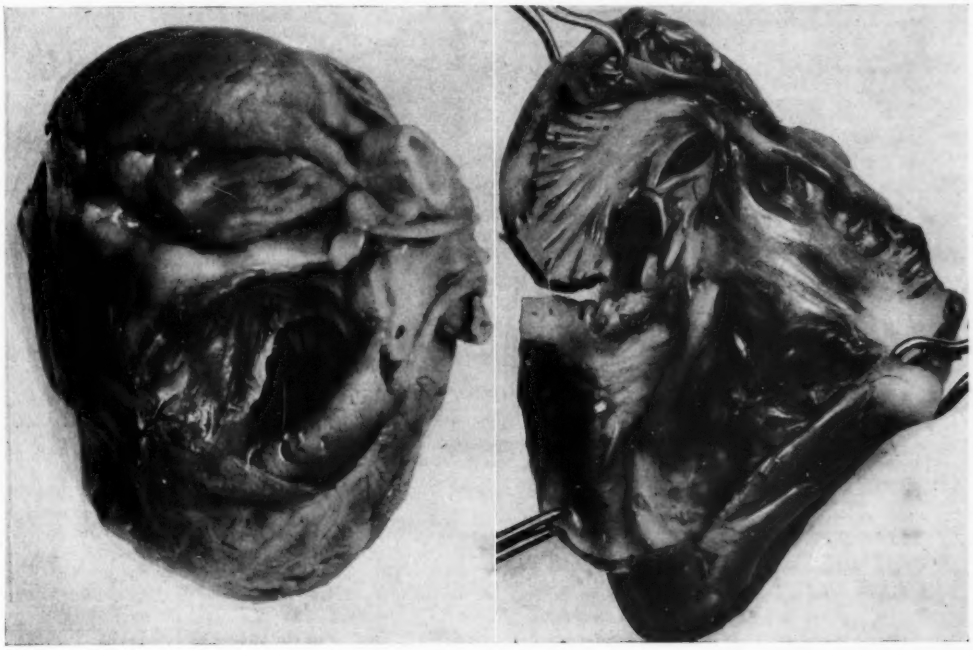

FIGURE VIIA FIGURE VIIB

Case II. (A) View of the heart from above and in front. The wall of the distal chamber has been stitched back to the left ventricle to show the sail-like "anterior" cusp and the communication with the proximal chamber. (B) Right lateral view showing the thickened walls of the right atrium, the atrio-ventricular ring, the proximal chamber of the right ventricle with its thin wall and the sail-like anterior cusp in front of it

distal chamber of the right ventricle from which the pulmonary artery springs is formed by the infundibulum proper and a cul-de-sac bounded by the anterior leaflet posteriorly and the anterior wall of the ventricle anteriorly. This chamber is dilated and the muscle walls measure only 1·5 millimetres in the thinnest part near the septum anteriorly and 4·0 millimetres laterally. The proximal chamber of the right ventricle communicates directly with the right auricle. It is bounded superiorly by the anterior cusp of the tricuspid valve and the communication with the upper chamber; medially by the septum and anteriorly and posteriorly by the ventricular muscle, which measures about 2·0 millimetres in average thickness.

The capacity of the upper chamber is approximately half that of the lower. The left auricle is normal—its wall measuring 2·0 millimetres in thickness. The mitral valve is normal. The left ventricle is 4·0 millimetres thick in its thinnest part and appears normal.

The coronary vessels are normal in origin and distribution.

Histological Findings. The muscle fibres of the left ventricle are fairly uniform in thickness and microscopically there is no abnormality.

The sections from the two chambers of the right ventricle are very similar. The walls are thin. The muscle fibres vary somewhat but the majority are comparable with those in the left ventricle. There is no fibrosis and the endocardium is normal.

Both lungs show fairly intense congestion of recent origin and diffuse emphysema.

There is very marked congestion of the liver which appears to be of recent origin in that there is no destruction of parenchymal cells in the centres of the lobules.

Case III

A female patient, aged eighteen years, was first seen on November 21, 1951. The patient stated that she was born blue. Her early childhood was uncomplicated by any major illness and she attended school at the normal age, but was never able to run about a great deal. At the age of fourteen she left school and was able to lead a quiet life. She now works at secretarial duties and attends a night business college. Exercise tolerance is reasonable, the patient being able to walk indefinitely at her own pace. Running brings on shortness of breath after twenty yards and if she persists, a tight sensation behind the centre of the sternum limits any further activity. When she stops this pain ceases in two to three minutes. The degree of cyanosis has not altered significantly since early childhood and is worse in cold weather and on exercise. Clubbing of the fingers and toes began at an early age but has not increased in degree over the last five years. The patient had never squatted. Menstrual periods are normal. There was no history of maternal rubella.

Physical Examination. The patient was a normally developed girl with moderate central cyanosis (grade III) and obvious clubbing of the fingers and toes. The pulse was of small volume and regular, rate 70 per minute. The systolic blood pressure was 105 millimetres of mercury. The diastolic pressure could not be obtained in the usual way as the sounds were so faint. Jugular venous pressure and wave form were normal. There was no chest deformity. The apex beat was in the fifth left intercostal space just outside the mid-clavicular line; it was well sustained but of small amplitude.

A quiet systolic pulsation without a thrill was felt in the second and third left intercostal spaces near the sternum. A quadruple rhythm was present, the additional sounds being of moderate intensity and

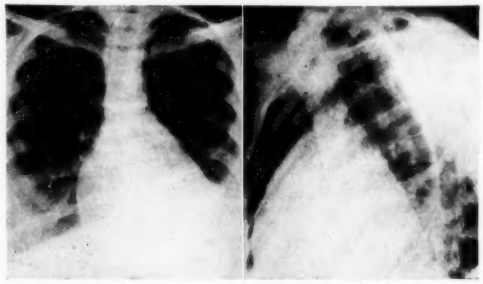

FIGURE VIIIA FIGURE VIIIB

Case III. (A) Postero-anterior and (B) left oblique view of the chest. There is considerable cardiac enlargement with a narrow pedicle and poorly vascularized lungs. There is dilatation of the right-sided chambers

heard down the left border of the sternum in mid-diastole and late diastole. The pulmonary second sound was normal. The remainder of the physical

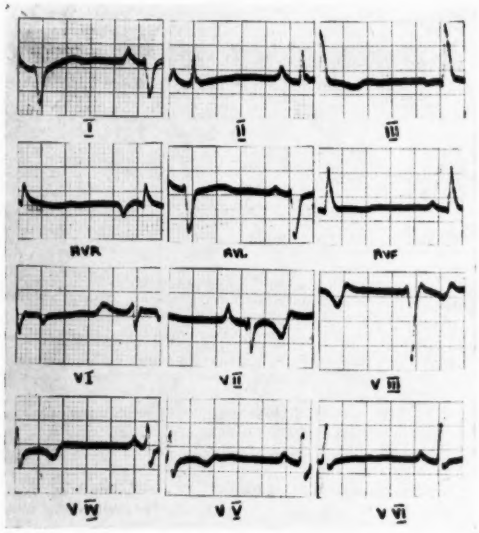

FIGURE IX

Case III. Electrocardiogram showing tall *P* waves and right bundle branch block. *PR* interval = 0·20 second, duration of *QRS* = 0·11 second. Sinus rhythm with occasional extrasystoles

examination gave normal findings. At a subsequent examination the rhythm was irregular, owing to extrasystoles shown by electrocardiogram to be

ventricular and nodal in origin. Some of the extrasystoles (? nodal) were accompanied by large jugular venous pulsations similar to the cannon waves seen in complete heart block.

The postero-anterior X-ray picture of the chest showed considerable enlargement of the heart (cardiothoracic ratio 0·63, Figure VIII). The right border appeared within normal limits and the enlargement was chiefly to the left. There was increased convexity of the right ventricular outflow tract. The aorta was left sided and the vascular pedicle narrow. The pulmonary artery and its branches were smaller than normal; the vascularity of the peripheral lung fields was diminished. In the left oblique view the anterior border extended forward almost to the chest wall and the posterior border backwards to overlap the spine.

These findings were confirmed at fluoroscopy and in addition prominent right auricular pulsation was evident.

The electrocardiogram (Figure IX) showed sinus rhythm with tall spiked *P* waves and right bundle branch block.

Case IV

A male patient, aged thirteen years, was first seen on February 8, 1952. This patient was known to have had heart disease since the age of four years. Examination at that time revealed a cardiac murmur which was considered significant. His early development was slow and he only began to walk at the age of eighteen months, and speech was not fully developed until the age of nine years. At eleven, when an anæsthetic was considered necessary for correction of strabismus, he was again examined and since then has been under supervision at the Royal Alexandra Hospital for Children. He is an active child, but has considerable limitation of exercise tolerance and in general tires towards the end of each day. There is no history of central chest pain, cyanosis, clubbing, palpitations or œdema. Previous illnesses included measles as a child, infective hepatitis at the age of twelve years, and two attacks of bronchitis when seven and nine years old. Operation for correction of divergent strabismus was performed at the age of eleven years. The patient has never had rheumatic fever.

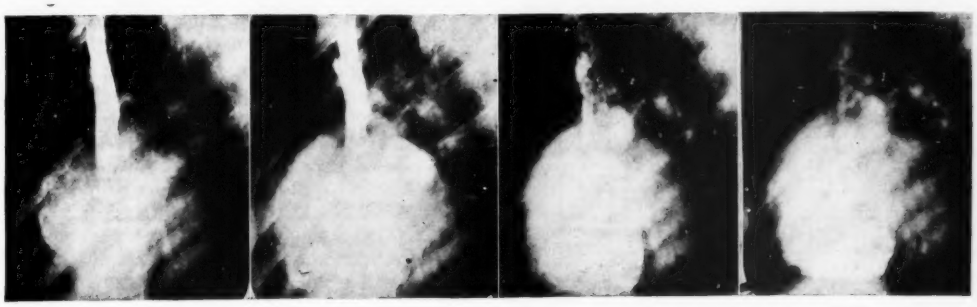

FIGURE X

Case III. Angiocardiograms, exposures at 1, 2, 4, and 6 seconds in the left oblique view. For description see case history.

The angiocardiogram (Dr. E. J. Halliday) (Figure X) was taken with the patient in the left oblique position and exposures were made at one second intervals from the beginning of the injection. In the first film dye could be seen in the right auricle and was beginning to fill the left auricle. It had also begun to fill the right ventricle but was not yet seen in the antero-inferior portion of this chamber, which was separated from the main body of the dye by a distinct line. In the second film dye completely filled both right sided chambers and the left auricle. The pulmonary artery and the left ventricle had also begun to fill. In all the subsequent films to six seconds the dye was still present in the right sided chambers and the pulmonary artery. The latter seems small. There was considerable speculation over the series and it was thought that the first film showed filling of the proximal chamber of the right ventricle, the unfilled antero-inferior portion representing part of the distal chamber. In the second film this cul-de-sac lying between the anterior wall of the right ventricle and the tricuspid valve had filled. The line of demarcation from the cul-de-sac probably represented the site of the tricuspid valve. There was gross delay in the emptying of the right side and the right to left shunt was thought to indicate a large *foramen ovale*. The aorta could be seen faintly in films three to six. The patient was considerably distressed by the injection of dye and a second injection was not given.

The family history was tragic and questionably significant. The patient was the youngest of six children, three of whom have already died. One brother died at the age of thirteen months from Ludwig's angina and another brother died suddenly at the age of six years after an injection of diphtheria antitoxin. The third brother, who was known to have heart disease, collapsed suddenly at the age of seventeen years while playing a quiet game of tennis.

Physical Examination. The patient was a restless male child, obviously mentally retarded and small for his age. The speech was slightly nasal and a marked divergent strabismus was present. There was peripheral cyanosis of the fingers, toes and cheeks, the latter giving a florid complexion. There was no clubbing of the fingers. The pulse rate was 80 per minute and irregular owing to frequent ectopic beats. The blood pressure was 90 millimetres of mercury, systolic, and 70 millimetres, diastolic. Femoral artery pulsations were present and the fundi were normal. The jugular venous pressure was normal. The palate was high and arched. The apex beat was not displaced and the cardiac impulse had a normal quality on palpation. No thrills were present. There was a faint systolic pulsation in the third left intercostal space near the sternum. On auscultation a moderate systolic and diastolic murmur was heard maximally in the fourth left intercostal space near the left sternal border. The diastolic murmur followed the third

heart sound. The second sound in the pulmonary area was widely split. The remainder of the physical examination gave normal findings. The electrocardiogram (Figure XII) showed an intermittent

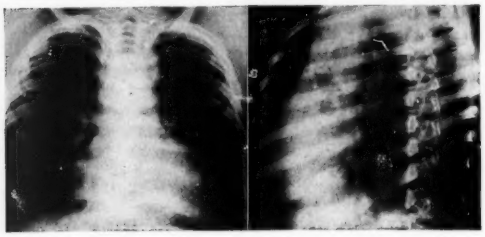

FIGURE XIA FIGURE XIB

Case IV. (A) Postero-anterior and (B) left oblique view of the chest. There is only slight cardiac enlargement due to dilatation of the right-sided chambers

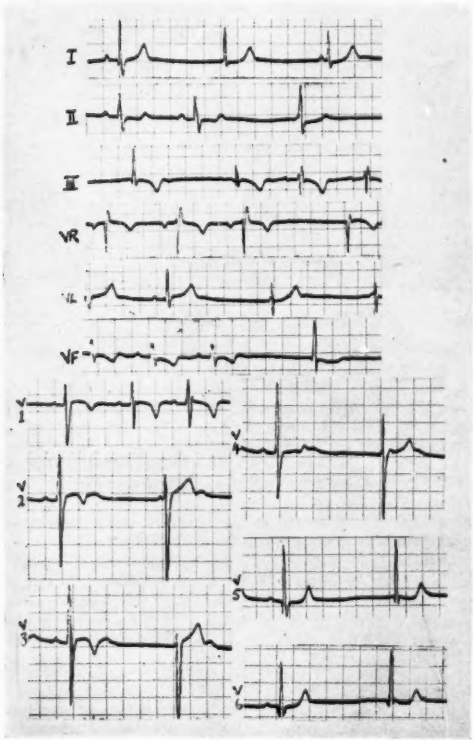

FIGURE XII

Case IV. Electrocardiogram showing sinus rhythm; sinus standstill and nodal escape. *PR* interval = 0·17 second. *QRS* = 0·09 second, with incomplete right bundle branch block pattern

incomplete right bundle branch block pattern with sinus standstill and nodal escape. On X-ray examination (Figure XI) the heart was not enlarged (cardiothoracic ratio 0·55), the left border being smoothly convex to the left. The right border, formed by the right auricle, was prominent. The aortic arch was left sided and the pulmonary vascular markings were normal. On fluoroscopy it was seen that the right auricle showed a forceful "presystolic" contraction and the infundibular portion of the right ventricle as seen in the postero-anterior view showed extremely vigorous systolic pulsations, which were not seen in the supradiaphragmatic portion of the same ventricle as seen in the left oblique position. The left auricle and left ventricle were not enlarged.

DISCUSSION

This is a rare malady but is perhaps not so uncommon as the small number of reported cases would suggest. At the time of writing at least twenty-eight cases proved by autopsy have been reported. The early reports, some of which are not readily available to us, have been summarized by Yater and Shapiro (1937), Walton and Spencer (1948), Engle, Payne, Bruins and Taussig (1950) and Baker, Brinton and Channel (1950). Since the publication of the last mentioned papers a case considered at autopsy to be Ebstein's disease has been reported in full by Giraux and Merlen (1951) and Paul, Myers and Campbell (1951) published the electrocardiogram of another in which autopsy was performed. In 1949 Tourniaire, Devrieux and Tartulier reported a case in a person still living in which the diagnosis was supported by cardiac catheterization, but we have been unable to see the original paper. Reynolds (1950) and Soloff, Stauffer and Zatuchni (1951) have also reported cases diagnosed during life, confirmation being obtained by angiocardiography. Of the 35 cases reported in full since the first in 1866, 23 have been written up in the last twenty-five years and perhaps more significantly 13 in the last three years, during which time interest in congenital heart disease has been more intense. There are in addition other cases which have not been reported in full (Paul, Myers and Campbell, 1951; Aegerter, 1951). It is therefore remarkable that no specimens of this condition were encountered by Keith (1909) in his series of 272 malformed hearts and only one by Abbott (1936) in her series of 1000 specimens.

Morbid Anatomy

The pathological reports of nearly all previous cases have demonstrated a remarkable similarity in the autopsy findings in the heart. In all cases, including our own Case II, the cusps of the tricuspid valve have been malformed, only one, or more rarely two, of the three cusps being functional. Nearly always the functional cusp has arisen in part from the vicinity of the

anterior portion of the atrio-ventricular ring and it is referred to as the " anterior " cusp. The remaining cusps, which have varied from case to case, have usually been rudimentary, small in size and adherent to the septal wall of the right ventricle. The " anterior " cusp, sometimes perforated by one or two openings, is fused in part with the anterior wall of the right ventricle. Another edge, continuous with the atrio-ventricular origin, is attached to the wall of the right ventricle below the muscular ridge which divides the right ventricle into the distal or infundibular portion and the proximal chamber. The free edge of this single functional cusp passes between the medial end of this upper attachment and the interventricular septum, and the valve exists as a sail-like membrane dividing the right ventricle into two chambers which communicate through the opening formed by the free edge of the cusp and the interventricular septum. Usually the *chordæ tendineæ* and papillary muscles are rudimentary. In addition to the valvular anomaly there is a maldevelopment of the right ventricular muscle which is well shown in Ebstein's illustration. In his case the unusual thinness of the right ventricular muscle appears to affect a large part of the wall of both parts of the ventricle. Engle *et alii* (1950) emphasized the thinness of the wall of the proximal chamber and thought that in their cases the thickness of the infundibular muscle was normal. In our own case the ventricular muscle next to the atrio-ventricular ring was well developed both below and above the tricuspid valve but the remainder of the anterior and posterior walls of the right ventricle was thin. In the case of Marxsen (1886) and probably that of Malan (1908) there was hypertrophy of the pulmonary conus. The significance of the defect of the right ventricular muscle, which is invariably present in some part of the right ventricle, will be discussed presently.

The right auricle was dilated in our own case as it has been in all others. We found the muscle hypertrophied, but in long-standing cases fibrosis may be found. The *foramen ovale*, although patent to a probe, was probably functionally closed; in the great majority of reported cases the *foramen ovale* has been patent, and the patient cyanosed. The pulmonary artery has always been normal or small, never large. The malformation is strictly confined to the right side of the heart.

The Ebstein type of tricuspid malformation is not the only anomaly of this valve, and Abbott (1936) illustrated another anomaly due to incomplete differentiation of the septal cusp. The electrocardiogram in Abbott's case appears to show incomplete right bundle branch block which, as will be seen later, is quite compatible with Ebstein's disease. Through the courtesy of Dr. R. M. Gibson, of the Royal Newcastle Hospital, we have seen another example of this anomaly of the septal cusp in a twenty-three years old girl who died of hypertension with auricular flutter and congestive cardiac failure. Prior to the onset of hypertension this patient had no symptoms.

The case of Graux and Merlen (1951) is unusual and does not conform to the classical description of Ebstein's disease. Pathologically the body of the right ventricle was " reduced to the size of a walnut and scarcely admitted two fingers ". The walls of the right ventricle and auricle were described as " not hypertrophied ". " The tricuspid valve is displaced towards the base, it is almost entirely formed of two cusps, the septal and the posterior meeting as a mitre, and both inserted in a normal manner around the atrio-ventricular ring. The anterior cusp is inserted lower down on the anterior wall of the ventricle, anchored by the papillary muscle." Clinically the case was remarkable in that the patient had no disability except for paroxysmal tachycardia, which led to his death at the age of seventy-two years. The heart was " normal to the ear and under the screen ". From the illustration it appears that the right ventricular wall was of normal thickness, and the clinical history certainly suggests that the right ventricle was competent. If this is a true variant of Ebstein's disease, it is possible that the dilatation of the right ventricle in the classical variety is secondary and depends on the position of the malformed cusp. However, the facts are too few to be dogmatic and we tentatively accept the view of Engle *et alii* that the true Ebstein anomaly consists of a malformation of the tricuspid valve with displacement of its origin into the right ventricle, which is dilated and of unusual thinness in one or both of its chambers.

Functional Pathology

In choosing for his paper the title " *Über ein sehr seltenen Fall von Insufficienz der Valvula tricuspidalis* ", Ebstein emphasized the insufficiency of the tricuspid valve seen terminally in his patient and noted in passing the defect in the right ventricular muscle. Cases seen before the onset of congestive failure (Yater and Shapiro, 1937; Bauer, 1945; Taussig, 1947; Reynolds, 1950) have not shown tricuspid incompetence and in the case of

Walton and Spencer (1948) the tricuspid valve was competent even in the presence of failure. Engle *et alii* also found no clinical or anatomical evidence in their three patients to support the presence of chronic tricuspid insufficiency during life. It is evident, therefore, that the malformed tricuspid valve functions efficiently and that tricuspid regurgitation is not an integral part of the syndrome.

The findings at catheterization in Case I are summarized in Table I. It was possible to pass the catheter from right auricle to pulmonary artery and back four times, and the opportunity was taken to explore thoroughly the proximal and distal chambers of the right ventricle. The thinness of the wall of the upper chamber or infundibulum was confirmed by the nearness of the tip of the catheter to the edge of the cardiac shadow. The proximal chamber extended on the left almost to the cardiac apex (Figure III).

The pressure tracings (Figure IV) were remarkable in that those taken in the pulmonary artery and in all parts of the right ventricle, both upper and lower chambers, were identical. The pressure in all three chambers was low. The change from a ventricular to an auricular pressure wave form occurred not at the junction of the proximal and distal ventricular chambers but at the presumed site of the atrio-ventricular ring. The right auricular pressure tracing showed a moderate auricular systolic wave, whose timing was confirmed by a simultaneous electrocardiogram. There was no evidence of tricuspid insufficiency. The rise of pressure in late diastole in the pulmonary artery was identical with that in the right ventricle and of similar magnitude to auricular systolic pressure. It, therefore, appeared likely that auricular systole initiated perfusion of the pulmonary circulation. In view of the relatively good exercise tolerance of this patient, the finding of a normal cardiac output and pulmonary blood flow was not unexpected. In a more severe case with cyanosis reported by Engle *et alii* the pulmonary flow was low and the systemic flow normal. No figures are available for the cardiac output during exercise in Ebstein's disease, but it is unlikely that it rises as much as in normal people during severe exercise. Indeed it is probable that the lack of right ventricular reserve plays a large part in determining not only the disability but also the high mortality associated with anæsthesia, surgical operations and arrhythmias.

The present findings suggest that the chief functional abnormality in this disease is the inadequacy of the right ventricle, which is unable to pump blood as well as a normal chamber. This inadequacy depends on the thinness of a large part of the ventricular muscle and the presence of a large sail-like membrane which divides the ventricle into two parts and so lessens the efficiency of both chambers, but particularly of the proximal one. During ventricular systole the tricuspid valve obstructs the tricuspid orifice at the atrio-ventricular ring, so preventing tricuspid regurgitation. This interpretation of the hæmodynamics of Ebstein's disease differs from that of Engle *et alii* whose cases were more severe. These authors believed that "during ventricular systole the misplaced tricuspid leaflets close the opening between the lower and upper chambers and the distal chamber sends the blood to the lungs", and "although the musculature of the auricularized right ventricle is thin and cannot exert much force, it seems probable that it too contracts during ventricular systole and sends the blood against the closed tricuspid valve, against the walls of the auricle and possibly through the *foramen ovale* to the left auricle". This hypothesis differs from our own chiefly as to the manner of closure of the tricuspid valve. These authors believe that during ventricular systole the right ventricle is divided into two chambers by the tricuspid valve and that the proximal chamber is in free communication with the right auricle. Our catheterization findings, however, support the view that the tricuspid valve, although malformed, carried out its normal function of separating the auricle from the ventricle in the vicinity of the atrio-ventricular ring; the identity of pressure in all parts of the right ventricle shows that the two chambers are in free communication. Whether or not systole is more effective in one chamber than the other we have no means of telling. The fluoroscopic findings in our Case IV did suggest, however, that ventricular emptying in that instance depended largely on contraction of the distal chamber. There is further evidence (van Lingen *et alii*, 1952) that the comparative narrowness of the opening between the distal and proximal chambers makes emptying of the latter more difficult than usual, especially if its walls become fibrosed in the later stages of the disease; the pooling of dye seen in this chamber at angiocardiography supports this concept. On examination of our specimen it can be seen that the "anterior" leaflet can easily be made to bulge into the tricuspid ring by pressure from above, and the functional evidence suggests that this was the probable method of closure

during life. Nevertheless the evidence is incomplete and confirmation of the present point of view must await further study.

Clinical Picture

As with most malformations of the heart, there is considerable variation in the degree of disability in Ebstein's disease. Our first, second and fourth patients were in fairly good health and although there was some disability, it was not a great handicap and did not prevent the first patient from leading a normal quiet life. The third patient was much more handicapped and was typical of most of those with cyanosis. Nevertheless she showed how much these patients can do in spite of cyanosis; Engle *et alii* have pointed out this discrepancy between cyanosis and exercise tolerance which distinguished Ebstein's disease from Fallot's tetralogy. In a severe tetralogy the patient is usually very cyanotic and unable to walk more than a few yards. In a mild tetralogy the colour may be normal at rest yet the exercise tolerance is still poor, and the patient benefits greatly from a Blalock-Taussig operation. In Ebstein's disease the patient is often moderately cyanosed at rest but is still capable of quite considerable effort.

The great majority of patients with Ebstein's disease have cyanosis, and it has been shown satisfactorily from an analysis of the records that this depends on patency of the *foramen ovale* (Engle *et alii*) and is therefore central in origin. Peripheral cyanosis, due to a low cardiac output, doubtless occurs and was described by the mother in our second case; it is either transitory depending on such things as cold weather, or if permanent, a terminal event. It is not accompanied by clubbing of the fingers as is usual in central cyanosis. Our third patient gave a history of central chest pain which satisfied the criteria of *angina pectoris*. In the second case of Baker *et alii* and also that of Reynolds there was a similar history. Although apparently frequent in Ebstein's disease, *angina pectoris* is not confined to this malformation and we have encountered it in other congenital lesions with marked right ventricular hypertrophy. The same may be said of a high arched palate which was also present in two cases.

In our cyanotic patient and also in the fourth patient, who was acyanotic, the pulse was of consistently low volume at rapid and slow rates. In one of them it was impossible to obtain a satisfactory diastolic pressure reading. This has been noted previously in cyanotic cases by Engle *et alii*, but does not seem to have been noted in acyanotic cases.

The jugular venous pulse has not been described fully in all phases of the disease, though Wood (1951*b*) remarks that it is usually normal. This too has been our experience, in spite of the presence of a larger auricular systolic wave than normal in the right auricular pressure trace (Figure IV). Why this wave does not become large enough to be seen in the neck is uncertain. A very large "*a*" wave in the jugular venous pulse is seen in severe pulmonary stenosis whether or not the *foramen ovale* is patent. Therefore it cannot be argued that in Ebstein's disease patency of the *foramen ovale*, by permitting an escape of blood into the left auricle, accounts for the absence of a large "*a*" wave, though it may lessen its amplitude. Very large "*a*" waves are found in three conditions: severe pulmonary stenosis, severe tricuspid stenosis and extreme pulmonary hypertension in which there is long-standing over filling of the right auricle (Wood, 1951). It would appear from one observation of Abrahams and Wood (1951) that effective auricular systole aids ventricular contraction. This is probably the case in Ebstein's disease, where under the fluoroscope the amplitude and rapidity of contraction of the right auricle, as seen in our present cases, is just as great as in severe tricuspid or pulmonary stenosis. But in Ebstein's disease there is little resistance to flow at the ticuspid or pulmonary valve and although auricular contraction is equally vigorous, the low resistance precludes the development of very high auricular systolic pressures. Confirmation of this was seen in our third patient, who suffered frequently from various arrhythmias. On one occasion she developed a series of nodal extrasystoles, while an electrocardiogram was connected. With each nodal beat there was a tremendous venous wave in the neck; presumably the closed tricuspid valve was providing the necessary resistance.

The protocols of reported cases show an extraordinary diversity of physical findings over the precordium. In some cases there were forceful pulsations or thrills, in others the precordium was quiet. In some the heart sounds were normal, while in others they were faint and in some there were loud murmurs or added sounds. In our own cases there was not this diversity of findings, but the picture was not identical from case to case. The first patient illustrated perhaps the most unobtrusive variety of Ebstein's disease as far as the physical findings were concerned and without the knowledge of the other findings she could have been passed as normal. There was, however,

a very weak but definite systolic pulsation in the fourth left intercostal space near the sternum and an inconstant soft systolic murmur in the same area. There were no added sounds and the pulmonary second sound was single. In the remaining three cases there were many points in common. In all of them there was a firm but gentle systolic pulsation over the outflow tract of the right ventricle, quite comparable to that sometimes seen in pulmonary stenosis. But whereas in the latter condition this pulsation may extend to the apex, in Ebstein's disease the thrust is localized to the

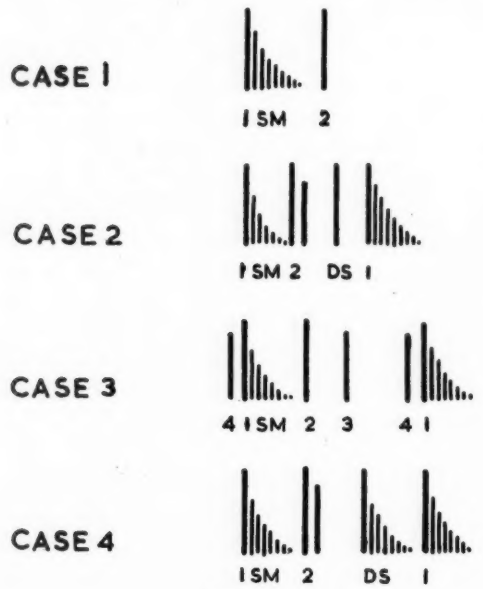

FIGURE XIII

Schematic representation of the auscultatory findings in our four cases of Ebstein's disease. SM = systolic murmur. DM = diastolic murmur. DS = diastolic sound

region of the outflow tract. Thrills were not felt in any patient. The heart sounds are represented schematically in Figure XIII. Except for the first case already discussed, in all cases added sounds were present. The slow rate in the third and fourth cases permitted easy analysis. In both there was a loud third sound early in the period of rapid ventricular filling. The third patient had in addition a presystolic sound equally as loud as the diastolic sound. The second patient had a loud diastolic sound, but because of the rate there was uncertainty about its nature. There was a soft parasternal systolic murmur in all four patients and the last patient had in addition a soft diastolic murmur following the diastolic sound; in fact the auscultatory findings corresponded with those of Baker's Case II. The phonocardiogram in that case illustrates what we feel must be a very frequent pattern in Ebstein's disease.

Engle *et alii* emphasized the faintness of the heart sounds in severe cases, though this has not been invariable in the experience of others. Baker *et alii* made no reference to this point. In our cases the intensity of the sounds was normal in the acyanotic cases and definitely diminished in the one cyanotic patient. In the cases of Yater and Shapiro and Reynolds the intensity of the heart sounds was also recorded as normal.

In previous cases (Ebstein, 1866; Marxsen, 1886; Schönenberger, 1903; Arnstein, 1927; Bassen, 1928; Bauer, 1945; Taussig, 1947) precordial thrills, systolic, diastolic or both were recorded, but they are more frequently absent than present. It seems most likely that the thrills and murmurs are produced by the movement of the tricuspid leaflet, and the passage of blood over its free edge. During ventricular systole the valve bulges into the atrio-ventricular ring and blood moves past its free edge, causing it to vibrate. In early diastole the valve moves away from the atrio-ventricular ring towards the base and there is a period of rapid ventricular filling. Prior to ventricular systole the valve floats back towards the atrio-ventricular ring. Thrills and murmurs are most likely to be produced at the time of the most rapid movement of blood, and of the valve leaflet, namely, during rapid ventricular filling and ventricular systole.

None of our patients had an enlarged liver, and in view of our earlier remarks this was to be expected because of the absence of tricuspid insufficiency or congestive failure.

ELECTROCARDIOGRAPHY

Full precordial electrocardiograms have been published by Baker, Brinton and Channell (1950), Reynolds (1950), Paul, Myers and Campbell (1951) and Soloff, Stauffer and Zatuchni (1951). These electrocardiograms closely resemble those of our first three cases, the main feature being high peaked *P* waves, delayed atrio-ventricular conduction time, and right bundle branch block of bizarre pattern. The secondary *R* wave in lead V1 is of low voltage. The electrocardiogram in Case IV did not show all these features. The rhythm was irregular owing to sinus arrest with nodal escape, and the right bundle branch block was

incomplete and intermittent. In precordial leads derived chiefly from the right ventricle the *T* waves were deeply inverted.

In the cases of Yater and Shapiro (1937) and Graux and Merlen (1951), the electrocardiogram shows left bundle branch block, which we are unable to explain. Yater and Shapiro showed that both branches of the bundle of His were normal. In all other cases in which the electrocardiogram was taken there was right bundle branch block.

The majority have normal sinus rhythm, but auricular, nodal and ventricular extrasystoles are frequent; paroxysmal tachycardia is not uncommon, and may be fatal (Yater and Shapiro, 1937; Taussig, 1947; Graux and Merlen, 1951).

RADIOLOGICAL FINDINGS

Perhaps the earliest X-ray photograph of a case of Ebstein's disease is that of Taussig (1947), taken when her patient was in comparatively good health. The film shows nothing characteristic and the heart was not enlarged. The films of the fourth and first patients show later but still early stages of the disease (Figures I and II). In the first patient the most striking features are the increase in transverse diameter (cardio-thoracic ratio, 0·6) due to dilatation of the right-sided chambers, the auricle as much as the ventricle. The convexity of the right auricle and of the infundibulum is particularly striking, and, though constant in all but the mildest cases such as Taussig's, it is by no means pathognomonic. The films of our remaining cases (Figures V and VIII) show the same features in a more striking way. The enlargement of the right side as seen in the left oblique view is so great that the right ventricle lies close to or in contact with the chest wall anteriorly and the left ventricle is pushed well back. With time the heart undoubtedly enlarged in a most striking way and the cases of Yater and Shapiro, Bauer, and Taussig, in which the patients were followed for some years, give convincing proof of this. Ultimately the cardio-thoracic ratio becomes as high as 0·8 and the heart fills a very large part of the thorax. In all our cases, as in those in which the point is mentioned in the literature, the aortic arch was left sided. The pulmonary artery is normal or small and must be distinguished from the infundibulum, which is invariably dilated. The vascular markings of the lung fields are normal or diminished.

Engle *et alii* have emphasized the remarkable quietness of the heart on fluoroscopy. In all their cases the hearts were grossly dilated. Our cases illustrate the earlier stages of Ebstein's disease and the fluoroscopic findings were rather different. The right auricular wall showed sudden sharp contractions and there was no doubt of the vigour of auricular systole. The proximal chamber of the right ventricle was always quiet and in two of the patients the movements of the dilated infundibulum were not impressive. But in the fourth patient, whose heart was the smallest of the series, the wide excursion of the infundibular wall during ventricular systole was striking and it seemed likely that in this patient the distal or infundibular chamber was largely responsible for the pumping of blood to the lungs.

The angio-cardiographic findings in our third case are in agreement with those previously reported (Baker *et alii*, 1950; Reynolds, 1950; Engle *et alii*, 1950; Soloff, Stauffer and Zatuchni, 1951). The outstanding feature is the enormous dilatation of the right side and the delay in emptying which usually exceeds 10 seconds (Figure X). In addition the patency of the *foramen ovale* is usually well demonstrated by the passage of dye into the left auricle in considerable amount. The pulmonary artery does not fill well in cyanotic cases because of the right to left shunt. The dilatation of the right sided chambers and the delay in emptying are both far greater than in any case of pulmonary stenosis we have encountered.

PROGNOSIS

Of the 13 reported cases in which death was presumably due to heart disease, the average age at death was twenty-six years. Of the 13 patients, four died suddenly. In 14 cases in which death was due to other causes as well, the average age was eighteen years. In four of these cases tuberculosis was found, while four patients died of other infections which might not have been fatal in people with normal hearts. Six died, some suddenly, following anæsthesia for thoracotomy, laparotomy or cardiac catheterization. Two patients have survived to sixty years of age (Marxsen, 1886; Malan, 1908) and one more to fifty-three (Walton and Spencer, 1948); these have all lived useful lives, one woman bearing two children. But these cases are clearly in the minority and it must be accepted that the majority of patients will die before thirty either directly of heart disease or of intercurrent infection. The risks from infection, whether tuberculous or not, should, of course, be much less now than formerly.

DIFFERENTIAL DIAGNOSIS

The clinical diagnosis of Ebstein's disease rests on the features which have been discussed above. The conditions which require differentiation fall into two groups; first, the various forms of pulmonary stenosis with or without overriding aorta, and, secondly, the group with enlargement of the cardiac silhouette.

In Ebstein's disease the history may closely resemble that of pulmonary stenosis with or without overriding aorta. In the acyanotic variety the history may be indistinguishable from that of "simple" pulmonary stenosis. In the cyanotic variety the patient is usually less handicapped than his degree of cyanosis would suggest. In this it differs from the cyanotic forms of pulmonary stenosis with or without overriding of the aorta (Engle *et alii*, 1950). The main physical findings which distinguish Ebstein's disease are as follows: a small radial pulse, a normal jugular venous pulse, a quiet heart to palpation without the signs of pronounced right ventricular hypertrophy, the presence of a triple rhythm, systolic and occasionally diastolic murmurs down the left border of the sternum, the bizarre electrocardiogram and characteristic radiological findings.

In Fallot's tetralogy the pulse volume is usually normal and there is a pronounced right ventricular pulsation and a systolic murmur which may be accompanied by a thrill in the left parasternal region. The heart is normal or slightly enlarged at fluoroscopy and enlargement, if present, is confined to the right ventricle. There is a concavity in the infundibular region, and in about 20% of cases the aortic arch descends on the right (Blalock, 1948). The electrocardiogram shows moderate right ventricular hypertrophy and the pattern is usually confined to lead V1.

In simple pulmonary stenosis with normal aortic root the symptoms and signs depend on the severity of the lesion. Mild pulmonary stenosis is common and the symptoms are not nearly so pronounced as in Ebstein's disease. The main distinguishing features of severe pulmonary stenosis are the large "*a*" wave in the venous pulse, the forceful right ventricular thrust, the almost invariable systolic thrill, the dilatation of the pulmonary artery except in the infundibular variety and often its left main branch in valvular stenosis, the rather small heart in spite of considerable right-sided hypertrophy, and the electrocardiographic pattern of extreme right ventricular hypertrophy with tall *R* waves and deeply inverted *T* waves extending from V1 as far as V4 or V5. In cardiac failure the heart of pulmonary stenosis may dilate considerably and the contour may be indistinguishable from that of Ebstein's disease, adding to the difficulty of differential diagnosis.

Amongst congenital malformations with a cardiac silhouette resembling that of Ebstein' disease are the group showing idiopathic hypertrophy of the heart (Wood, 1950) or familial cardiomegaly (Evans, 1947). As a group they lack the positive features of Ebstein's disease and at times have distinguishing features of their own. There are two acquired forms of heart disease with an X-ray silhouette resembling that of Ebstein's disease. They are pericarditis with effusion and acute infective myocarditis with extreme cardiac dilatation. In pericarditis the friction rub may resemble the murmur of Ebstein's disease, and the faint heart sounds, triple rhythm, weak pulse and decreased pulsation under the fluoroscope have in the past added to this confusion. The venous pressure is greatly elevated, the liver may be enlarged and the cardiac contour may change with posture. The electrocardiogram is not that of Ebstein's disease and has distinguishing features of its own. In case of difficulty a catheter may be passed into the right auricle to show the separation of the auricular wall from the edge of the cardiac shadow (Wood, 1951).

Acute infective myocarditis and dilatation of the heart may be primary or secondary to infection elsewhere. The cardiac silhouette may closely resemble that of Ebstein's disease and the small pulse and gallop rhythm can prove confusing. There is no previous history of heart disease and the electrocardiogram differs in both the *QRS* and *T* wave changes. In conclusion it can be seen that the diagnosis of Ebstein's disease depends not on any single feature but on a careful consideration of the history, the physical examination, the electrocardiogram and the fluoroscopic findings. It is important to distinguish it from conditions which can be relieved by surgery, for reports of attempted pulmonary valvulotomy or systemic-pulmonary anastomosis have not been encouraging. Although plastic operations on the tricuspid valve are technically possible, it is unlikely that restoration to normal of the tricuspid valve alone would correct a malformation in which the ventricular muscle is also involved.

SUMMARY

1. Ebstein's disease is a congenital malformation of the heart in which the origin of the tricuspid valve is partially displaced from the

atrio-ventricular ring into the right ventricle. The cusps are malformed, one or more usually, two of them being rudimentary. The single functional cusp divides the ventricle into two chambers which communicate between the free edge of the cusp and the ventricular septum. Part of the wall of the right ventricle is also malformed. Until it is shown that the typical valvular deformity can exist without the abnormality of the right ventricle it is suggested that the term Ebstein's disease be reserved for malformations affecting both the valve and the muscle, in order to distinguish it from other malformations affecting the tricuspid valve.

2. The tricuspid valve is usually competent and tricuspid insufficiency is only a terminal event in the majority of cases. Because of the deformity of the valve which hinders emptying, and the muscle which limits the force of systole, right ventricular contraction is inefficient and the cardiac reserve is low. The two chambers of the right ventricle are in anatomical and functional communication at all times, but there is some evidence that the distal or infundibular chamber contracts more efficiently. Because of the weakness of the right ventricle, dilatation and hypertrophy of the right auricle are invariable.

3. Cyanosis depends on the elevation of pressure in the right auricle relative to that in the left and the presence of a patent *foramen ovale*. It is not an integral part of the syndrome.

4. The severity of the symptoms and the rate of deterioration vary considerably, as do the clinical signs; survival to sixty years has been recorded, though this is unusual.

5. In all but the mildest cases the clinical diagnosis can be made with fair certainty and depends on the following features: (*a*) Enlargement of the right side of the heart which may be progressive. Radiologically the right auricular curve is increased and until the terminal stages are reached shows considerable activity. The infundibulum of the right ventricle is dilated and may also show considerable activity. This has its clinical counterpart in the systolic pulsation to the left of the mid-sternum. The proximal chamber of the right ventricle is less active and the overlying chest wall is correspondingly quiet. (*b*) The peripheral arterial pulses are often weak. The venous pulse is normal. (*c*) Triple rhythm probably occurs in all but the mildest cases. The heart sounds may be faint. (*d*) The precordial electrocardiogram shows right bundle branch block which does not conform to the classical description, in that the secondary *R* wave in right ventricular epicardial leads is not tall. Arrhythmias are frequent and may be fatal. Murmurs and thrills are not essential but when present may be systolic and diastolic. (*e*) Confirmation of the diagnosis can be obtained during life by cardiac catheterization or by angiocardiography. The latter method has the advantage that the films show a characteristic picture of right ventricular dilatation and delay and may even demonstrate the abnormal valve cusp. Angiocardiography has the disadvantage that it is inherently a slightly more dangerous procedure than a properly performed cardiac catheterization. (*f*) Because of the inherent weakness of the right ventricle it is suggested that plastic operations on the tricuspid valve would probably not benefit the patient.

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BIBLIOGRAPHY

ABBOTT, M. E. (1936), "Atlas of Congenital Cardiac Disease", New York, American Heart Association, page 44.

ABRAHAMS, D. G., and WOOD, P. (1951), "Pulmonary Stenosis with Normal Aortic Root", *Brit. Heart J.*, **13**, 519.

AEGERTER, E. E. (1951), quoted by Soloff, Stauffer and Zatuchni.

ARNSTEIN, A. (1927-28), "*Eine seltene Missbildung der Trikuspidalklappe (Ebsteinsche Krankheit)*", *Arch. path. Anat.*, **266**, 247.

BAKER, C., BRINTON, W. D., and CHANNELL, G. D. (1950), "Ebstein's Disease", *Guy's Hosp. Rep.*, **99**, 247.

BASSEN, J. (1928), quoted by M. E. Abbott, "Blumer's Bedside Diagnosis", **3**, 482.

BAUER, D. DE F. (1945), "Ebstein's Type of Tricuspid Insufficiency: Roentgen Studies in a Case with Sudden Death at the Age of Twenty Seven", *Am. J. Roentgenol*, **54**, 136.

BLALOCK, A. (1948), "Surgical Procedures Employed and Anatomical Variations Encountered in the Treatment of Congenital Pulmonic Stenosis", *Surg., Gynec. and Obst.*, **87**, 385.

EBSTEIN, W. (1886), "*Über einen sehr seltenen Fall von Insufficienz der Valvula tricuspidalis, bedingt durch eine angorebene hochgradige Missbildung derselben*", *Arch. Anat. Physiol. u. wissenschaft. Med.*, 238.

ENGLE, M. A., PAYNE, T. P. B., BRUINS, C., and TAUSSIG, H. B. (1950), "Ebstein's Anomaly of the Tricuspid Valve", *Circulation*, **1**, 1246.

EVANS, W. (1947), "Familial Cardiomegaly", *Brit. Heart J.*, **9**, 309.

GRAUX, P., and MERLEN, J. F. (1951), "*À propos d'un cas de maladie d'Ebstein*", *Arch. d. mal. du cœur*, **44**, 263.

KEITH, A. (1909), "The Hunterian Lectures on Malformation of the Heart", *Lancet*, **2**, 395.

MALAN, G. (1908), "*Über die Enstehung eines Herzgeraüsches*", *Centralbl. f. allg. Path. u. path. Anat.*, **19**, 452.

MARXSEN, T. (1886), "*Ein seltener Fall von Anomalie der Tricuspidalis*", Inaug. Diss. Kiel.

PAUL, O., MYERS, G. S., and CAMPBELL, J. A. (1951), "The Electrocardiogram in Congenital Heart Disease: A Preliminary Report", *Circulation*, **3**, 564.

REYNOLDS, G. (1950), "Ebstein's Disease: A Case Diagnosed Clinically", *Guy's Hosp. Rep.*, **99**, 276.

SOLOFF, L. A., STAUFFER, H. M., and ZATUCHNI, J. (1951), "Ebstein's Disease", *Am. J. M. Sc.*, **222**, 554.

SCHÖNENBERGER, F. (1903), "*Über einen Fall von hochgradiger Missbildung der Tricuspidaklappe mit Insufficienz derselben*", Inaug. Diss. Zurich.

TAUSSIG, H. B. (1947), "Congenital Malformation of the Heart", New York, Commonwealth Fund, page 520.

TOURNIAIRE, A., DEVRIEUX, F., and TARTULIER, M. (1949), "*Maladie d'Ebstein, essai de diagnostic clinique*", *Arch. d. mal. du cœur*, **42**, 1211, quoted by Graux and Merlen, *loc. cit.*

VAN LINGEN, B., McGREGOR, M., KAYE, J., MEYER, M. J., JACOBS, H. D., BRAUDO, J. L., BOTHWELL, T. H., and ELLIOTT, G. A. (1952), "Clinical and Cardiac Catheterization Findings Compatible with Ebstein's Anomaly of the Tricuspid Valve: A Report of Two Cases", *Am. Heart J.*, **43**, 77.

Walton, K., and Spencer, A. G. (1948), "Ebstein's Anomaly of the Tricuspid Valve", *J. Path and Bact.*, **60**, 387.

Wood, P. (1951*a*), "Disease of the Heart and Circulation", Eyre and Spottiswoode, London.

Wood, P. (1951*b*), personal communication.

Yater, W. N., and Shapiro, M. J. (1937), "Congenital Displacement of the Tricuspid Valve (Ebstein's Disease): Review and Report of a Case with Electrocardiographic Abnormalities and Detailed Histologic Study of the Conduction System", *Ann. Int. Med.*, 40, 1043.

ADDENDUM

Since this article was written the following case has been investigated in this clinic and the criteria as already stated for the clinical diagnosis of Ebstein's disease appeared to be fulfilled. For that reason, a short clinical summary is included.

CASE V.—A male patient, aged thirteen years, was first seen on February 28, 1952. This boy was seen in the first month of life by a Japanese doctor in Tokyo, who suspected the presence of congenita heart disease, His mother, a Russian who had married an Australian sea captain, had been worried by the child's restlessness and inability to thrive. Further medical advice obtained in Singapore, when the child was four months old, had endorsed this opinion, the mother being informed that an abnormal murmur was present. Cyanosis was apparently not noticeable at that time. Over the years the child was slow to develop and from the age of five increasing physical handicap had become manifest. At the time of the present examination the patient was able to walk slowly without distress, but running or extreme exertion was impossible. Effort was always limited by dyspnœa, but at times central chest pain, satisfying the criteria of ischæmic cardiac pain, would occur.

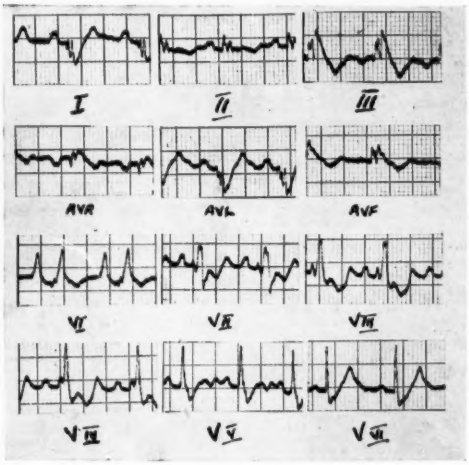

FIGURE XIV

Case V. Electrocardiogram showing tall *P* waves and right bundle branch block. *PR* interval = 0·15 second, duration of *QRS* = 0·15 second

The mother was unconscious of any abnormal colour in the child's appearance, but on careful questioning it appeared that permanent cyanosis had appeared between the eighth and tenth years. She had been unconscious of the onset of clubbing. There was no history of squatting, palpitations or œdema. It was the mother's opinion that the child's exercise tolerance had diminished somewhat over the preceding twelve months and that he was more tired than usual. There had been no important illnesses in the past and the patient's brother, five years his senior, was quite well. The mother had suffered from no illness during this pregnancy.

Physical Examination. The patient was an intelligent but nervous boy, somewhat reserved. Central cyanosis was manifest by mild clubbing of the fingers and toes and blueness of the tongue and suffusion of the conjunctivæ. The palate was normal. The pulse was regular but of small volume, the systolic blood pressure being 105 millimetres of mercury. It was impossible to obtain an accurate diastolic reading. The jugular venous pressure was slightly elevated, an analysis of the wave form showing a predominant systolic regurgitant wave. The cardiac

impulse was displaced to the anterior axillary line, and was soft and undulating in quality. A mild systolic thrill was present in the fourth left intercostal space just lateral to the sternal border. A systolic expansile pulsation was detectable in the third left intercostal space, but nothing was felt in the second

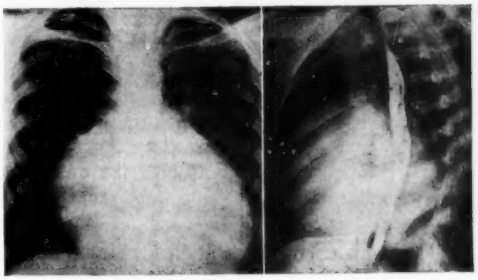

FIGURE XV

Case V. Postero-anterior and left oblique views of the chest showing enlargement of the heart (cardio-thoracic ratio=0·64) due to dilatation of the right auricle and ventricle

left intercostal space, the usual site of pulmonary artery pulsations. In the third and fourth right intercostal spaces presystolic pulsations occurred, which were interpreted as arising from the contractions of the right auricle. On auscultation a Grade 3 systolic murmur was heard maximally at the site of the above thrill. This was followed by a widely split second sound with an additional third sound heard easily in mid diastole. There were no diastolic murmurs. The pulmonary second sound was widely split. The liver was not enlarged and no pulsations were felt. The remainder of the physical examination gave normal findings.

The red cell count was 6·04 million per cubic millimetre and the hæmoglobin content 19·5 grammes *per centum*. The white blood cell count was normal. The electrocardiogram (Figure XIV) showed the presence of right bundle branch block, the *QRS* complexes being 0·16 second or more in duration. Prominent tall spiked *P* waves were present in lead V1. X-ray examination revealed (Figure XV) a greatly enlarged heart (cardio-thoracic ratio, 0·64) with markedly convex right and left borders. The right border was composed of a large right auricle, the displacement of the left, being due to a prominent conus of the right ventricle. In the left oblique view the ventricular shadow did not clear the thoracic vertebral bodies and had a *cœur-en-sabot* appearance. The vascularity of the lung fields appeared diminished. On fluoroscopy the enlarged right auricle showed accentuated presystolic contractions and the main right ventricular movement appeared to occur in the infundibular region. The left side of the heart was normal.

This case differs in no fundamental respect from those already described. It represents a more advanced stage of the disease in which the heart has increased in size, considerable central cyanosis has developed as a result of a right to left shunt through a patent *foramen ovale*, and early tricuspid insufficiency has developed. The X-ray appearances and electrocardiogram differ only in degree from the previous illustrations and the findings on palpation and auscultation are almost identical. It is of interest that the thrill and maximal intensity of the sounds and murmurs occurred in the presumed region of the tricuspid leaflet. The case is unusual in that right auricular pulsations were readily detectable on palpation to the right of the sternum.

VASCULAR ABNORMALITIES OF THE LUNG

CYRIL FORTUNE
Perth

IT is important that physicians and surgeons should be clearly aware of the vascular abnormalities which may occur in the lung. The clinical and radiological pictures to which they give rise may cause considerable difficulty and error in diagnosis unless these malformations and congenital defects are appreciated.

A classification is attempted in the following tabulation which lists abnormalities found in the pulmonary artery and its branches, the capillary network and the pulmonary veins:

1. Pulmonary arteries:
   - (*a*) Pulmonary artery aneurysms.
   - (*b*) Abnormal anastomoses associated with pulmonary artery atresia.
   - (*c*) Anatomical variation in segmental distribution of vessels.
2. Sequestration of lung tissue:
   Associated with abnormal vessels.
3. Pulmonary telangiectases:
   Arterio-venous fistulæ.
   Arterio-venous aneurysms.
4. Anomalies of pulmonary veins.
5. Abnormal bronchial vessels.
6. Primary pulmonary hypertension:
   - (*a*) Due to congenital dilatation of the pulmonary artery.
   - (*b*) Due to bronchial arterial anastomoses.

PATHOGENESIS OF VASCULAR ANOMALIES

Mesodermal dysplasia gives rise to vascular malformation. Sabin (1922) found that blood vessels spread over the developing embryo in definite sheets of capillaries. In primitive vessels, after circulation has begun, a certain vessel can serve as an artery and then change to form a capillary plexus. Conversely, the vessel can serve as a vein, and subsequently receive new arterial connexions and become an arterial plexus with change of flow of the blood.

Thompson and Shafer (1951) consider that the abnormal development of arteries and veins from the capillary plexus affords a rational explanation for the occurrence of vascular anomalies, and this is seen in a striking way in the malformations which occur in the lung; but it must not necessarily be accepted that these anomalies are all congenital. There is evidence that they may be developmental in origin and prone to increase in size owing to humoral factors acting before or after birth and even later in life.

The main discussion will be concerned with the clinical appreciation of pulmonary telangiectasis; but some reference to the other abnormalities will be made at the outset.

PULMONARY ARTERIES

Pulmonary Artery Aneurysms

Deterling and Clagett (1947) have carefully recorded their findings and given a comprehensive account of the causation of pulmonary artery aneurysms. They point out that 47% are congenital in origin, and in one-fifth of these cases the defect was associated with patent *ductus arteriosus*, and in some other cases with a ventricular septal defect. They stated that it was important to remember that, in a patient who had a patent ductus, there might be associated evidence of pulmonary artery aneurysm. Other causes were syphilis, infected emboli, atheroma, occasionally trauma and mycotic degeneration of the arterial wall due to subacute bacterial endocarditis (Lillian, 1949).

In the secondary branches of the pulmonary artery aneurysms may form owing to bronchiectasis, or in the case of chronic tuberculosis, Rasmussen's aneurysm may be present in the walls of cavities in 4% to 5% of subjects which come to necropsy.

Abnormal Anastomoses Associated with Pulmonary Artery Atresia

In pulmonary artery atresia abnormally large bronchial arteries are found, and these may anastomose directly with branches of the pulmonary artery at the lung hilum. In this condition, too, other vessels may supply the lung from the pericardial, œsophageal and internal mammary anastomoses.

Anatomical Variations in Segmental Distribution of the Pulmonary Artery

Although there is a standard plan of division of each pulmonary artery, there are minor variations, as well as a wide range of anastomoses, the nature of which is of great importance to the surgeon in operations on the lung.

SEQUESTRATION OF LUNG TISSUE ASSOCIATED WITH ABNORMAL VESSELS

Sequestration of the lung tissue is a condition usually associated with abnormal vessels.

Pryce (1946), Bruwer *et alii* (1950) and D'Arcy Sutherland (1950) stress the fact that whenever cystic disease of the lower lobe is recognized and operation contemplated, the presence of abnormal vascular connexions is of paramount importance to the surgeon.

The abnormal vessels which arise from the dorsal aorta are usually found coming from the lower thoracic aorta, the upper abdominal aorta or the cœliac axis. In the developmental period of these vessels they sequestrate a portion of the developing lung bud. Thus, the abnormal artery may supply normal lung, or sequestrated and normal lung, or sequestrated lung only.

If the abnormal vascular connexion disappears, the sequestrated lung becomes a localized congenital cystic mass, showing as a circumscribed opaque area at the base of the mediastinum, usually on the left side.

Failure to recognize these abnormal arteries (often coming through the diaphragm) has led to fatal hæmorrhage in cases of lower lobe lobectomy (Harris and Lewis, 1940).

ANOMALIES OF THE PULMONARY VEINS

Brantigan (1947) has indicated the surgical significance of anomalies of the pulmonary veins.

In these cases, it is usually found that the total drainage from the lung is to the right atrium, or else partly to the right atrium and partly to the superior *vena cava* and left innominate vein. It is a shunt of arterial blood back into the venous system. If this occurs, the patient can be benefited by removal of the portion of the lung thus drained, although usually there is no evidence of failure of the right side of the heart.

There may be a number of anomalous veins draining into the left atrium. It is thus important in individual ligation technique for lobectomy of the lung to demonstrate the presence of more than one pulmonary vein if devitalization of the whole lung is to be avoided.

ABNORMAL BRONCHIAL VESSELS

In the lungs there is a double blood supply derived from the bronchial and pulmonary systems. This extends as far as the respiratory bronchioles. There is evidence that in adult life anastomoses can develop between the bronchial artery and the pulmonary artery. Wood and Miller (1938) and Marchand, Gilroy and Wilson (1950) have shown in the human cadaver greatly increased communications in the form of large vascular shunts between the bronchial and pulmonary arterial systems in certain instances of pulmonary cardiac disease.

It is considered that often the cause of hæmoptysis in pulmonary telangiectasia is due to increase in pressure and rupture of small anastomosing vessels between the pulmonary and bronchial arteries (Lendrum *et alii*, 1950).

Brinton (1950) suggests that an abnormal bronchial arterial circulation may be present in primary pulmonary hypertension.

In cyanotic congenital heart disease there is evidence of well-defined, increased collateral bronchial circulation in some instances.

PRIMARY PULMONARY HYPERTENSION

Primary pulmonary hypertension is a well-defined condition which occurs in middle-aged people and sometimes in the earlier age group, and it is considered to be due to early endarteritis of the smaller vessels of the pulmonary artery. This endarteritis occurs over foci of aplasia and hypoplasia of the media of the arterial wall and the lesser pulmonary circulation. William Evans (1951) found this condition associated with congenital dilatation of the pulmonary artery and its branches. On the other hand, Brinton (1950) has suggested that the primary pulmonary hypertension may result from an abnormal amount of blood flowing from the bronchial arteries into the lesser circulation, this blood being injected under pressure causing dilatation and sclerotic changes to the pulmonary artery with hypertrophy and, later, evidence of failure of the right side of the heart.

It is interesting to conjecture that, if this theory is correct, ligation of a portion of the bronchial arterial supply may cause some retrogression of primary pulmonary hypertension if the condition was recognized early enough.

PULMONARY TELANGIECTASIA

The condition of pulmonary telangiectasis is more frequently called arterio-venous aneurysm or arterio-venous fistula of the lung. Whitaker

(1947), Hayward and Reid (1949) and Brink (1950) prefer the term " telangiectasis ". There are sound reasons why this term is more suitable. The presence of arterio-venous shunts by-passing the capillary circulation in the human lung has been suspected from the fact that certain parasites can pass through the lung, and also from blood gas analyses.

Proof has been furnished by the pathological reports following lobectomy for this condition.

Prinzmetal *et alii* (1948) have shown in experimental animals that glass spheres, many times the accepted diameter of capillaries, will pass through the pulmonary vessels of the dog and rabbit.

Tobin and Zariquiey (1950) found in isolated human lungs arterio-venous shunts many times the accepted diameter of capillaries, by the passage of glass spheres from the pulmonary artery to the pulmonary vein.

These shunts are usually located at the apex and within the lobular division of the lung, but experimentally no shunts were demonstrable in the hilar region or along the course of the larger pulmonary veins and arteries.

It is conceivable that these small arterio-venous shunts are quiescent, but that in pathological states (such as emphysema and pulmonary fibrosis) they may increase in size.

On the other hand, the congenital or developmental type of arterio-venous shunt is usually situated towards the hilar region. It is a large, vascular cavity in direct communication with one or two dilated branches of the pulmonary artery and vein. The cavity is usually lined with a single layer of endothelial cells, and the wall consists of collagenous connective tissue. The entering artery has a large amount of elastic tissue in its structure. A proportion of the venous blood in the pulmonary artery passes through the aneurysmal sac to the pulmonary vein. Therefore, this blood is not aerated in the lungs and it is returned to the systemic circulation incompletely saturated with oxygen. This arterial hypoxia leads to the development of secondary polycythæmia, cyanosis, " clubbing " of the fingers and dyspnœa on effort. The increased blood volume is due not to plasma, but to increased red cell mass.

This indicates that these shunts are different in structure and function from the arterio-venous shunts found (especially in the leg) after trauma, in which there is an increasing blood volume due to increased plasma, and therefore increasing strain on the heart.

Three cases are presented which will illustrate the natural history of this abnormality, define clearly the clinical syndrome, illustrate the complications which may occur and show that thoracic surgery offers a complete cure.

CASE I.—A printer, aged thirty-eight years, was referred for diagnosis. The history given was that his mother was anæmic while carrying her child. He was fit and well up to the age of nine years and able to use his bicycle, and was accepted as a normal child. About this time he was responsible for an accident to his sister. Two days later he had several " turns ", and when he fainted he was said to " go black in appearance ". His doctor recognized " clubbing " of the fingers at this age, although his general colour was said to be normal.

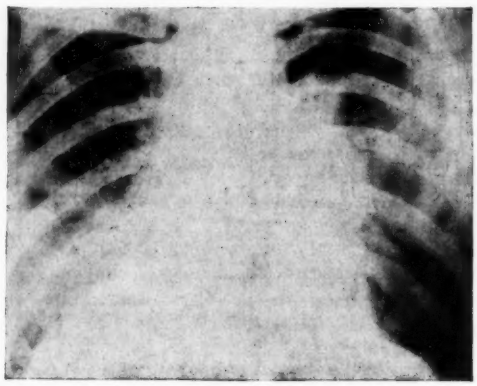

FIGURE I.

Case I, 1934. The lobulated opaque areas seen in both hilar regions were considered to be due to enlarged glands.

He progressed through school and reached the junior standard. During the next eleven years he served his trade and lost no time through ill-health, but when he was aged twenty-eight years he had an apparent attack of gout in the right great toe; on occasions this has recurred, usually lasting from two to seven days, but clearing up on the exhibition of a suitable mixture. The patient's grandfather had suffered from gout.

During his late 'teens it became apparent to his relatives and friends that his skin was changing to a " bluish tint ", and medical advice was sought in the year 1934. He was then diagnosed as suffering possibly from enlarged mediastinal glands.

In 1935 he was reexamined and a diagnosis was made of congenital heart disease with secondary polycythæmia. He continued to lead a normal life until November 1948, when he experienced a peculiar " turn ". He became numb and physically paralysed and unable to speak. This condition lasted for ten minutes. He recovered his speech, but the weakness in his hands recovered more slowly.

He was admitted to hospital and the same experience occurred again on the day of examination—he felt " something coming over him ", his voice was weak, he experienced a feeling of limpness and fell to the ground. When he was picked up, he was " blue in

appearance" and "felt terrible". Except for transitory tightness in the chest, he had had no precordial pain; but he had complained of some shortness of breath and mild giddy spells previous to this last attack. Nose bleeding rarely occurred.

On physical examination of the patient the outstanding features were cyanosis, "clubbing" of the fingers and toes, and congestion of the conjunctivæ. No nævi or telangiectatic nodules were found. The retinal vessels were tortuous and congested.

Examination of the heart revealed normal loud first and second sounds, but a grade II systolic murmur was heard over the precordium and the lateral aspect of the chest wall anteriorly. It was louder on inspiration. His blood pressure was 112 millimetres of

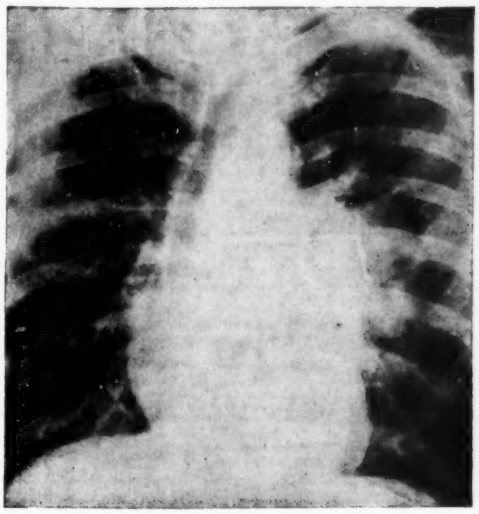

FIGURE II.

Case I. The postero-anterior projection of the chest in 1948 showed no significant alteration in the radiographic appearances. At fluoroscopic examination the opaque areas were now recognized as exhibiting expansile pulsation, and were considered therefore to be probably vascular.

mercury, systolic, and 98 millimetres, diastolic. The spleen was palpable and enlarged to one finger's breadth below the costal margin. Pigmentation was present on both legs.

A radiological examination was made (Figures I to III), and the radiologist reported as follows:

> In view of the apparent coexistence of two conditions (the presumed cardiac defect and the gland mass), for neither of which a satisfactory explanation could be offered, review of the films of this case was undertaken.
>
> This review suggested that the shadow extending upwards from the upper pole of the "gland mass" might, in fact, be an enlarged blood vessel.
>
> This feature is particularly well seen in the right anterior oblique view (December 30, 1948), where the shadow is seen to curve upwards and backwards from the principal lesion. The resemblance to a large vessel entering the lesion suggested that the shadows might all be vascular.
>
> The possibility of a hæmangioma with gradual dynamic expansion over the years, together with the formation of sacs and arterio-venous fistulæ, was postulated.
>
> The tomogram films supported this suggestion of sac formation.
>
> Subsequent screening showed definite expansile pulsation of both the vessel already described and the upper part of the main shadow.
>
> On the above grounds, this diagnosis of hæmangioma with arterio-venous fistulæ of the pulmonary circulation is offered.
>
> The lateral view suggests that the upper lobe of the left lung is the site of the lesion. Both the lingular and the pectoral (antero-lateral) broncho-pulmonary segments appear to be involved.

It was possible to compare with these films the films taken fifteen years previously, and a similar appearance was present in both films.

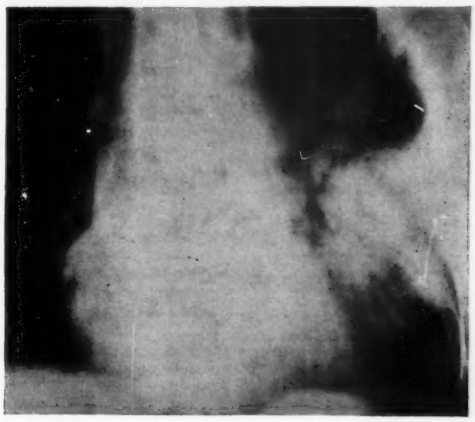

FIGURE III.

Case I. Tomogram studies suggest that the site of these saccular vascular dilatations is the upper lobe of the left lung, both lingular and anterolateral pulmonary segments being involved.

The laboratory findings indicated a severe grade of polycythæmia; the hæmoglobin value was 23 grammes *per centum* and the erythrocytes numbered 8,760,000 per cubic millimetre.

The whole picture crystallized and fitted well into Burchell and Clagett's clinical syndrome (1947) of pulmonary arterio-venous fistula.

Surgical exploration was carried out by Dr. C. J. Officer Brown, of Melbourne, on February 22, 1949. The left pleural cavity was opened after removal of the sixth rib. A tense, bluish-red cystic tumour was present in the lingula and the lower portion of the pectoral segment. It was the size of a tennis ball, lobulated and pulsating vigorously. A continuous thrill was present. The tumour bulged beyond the lung surface on its mediastinal aspect, and on the costal surface a number of small, rounded elevations were present. The wall was thin and blood could be seen swirling within the lumen. No other vascular tumours were seen in the left lung.

In view of the size of the fistula, upper lobectomy was performed. The main pulmonary artery and the superior pulmonary vein were large and thick-walled.

A considerable amount of anastomotic circulation was present in the region of the vascular pedicles. After ligation of the upper lobe arteries, the tumour became flaccid and the thrill and pulsation ceased.

The post-operative course was smooth, except for pronounced tachycardia for three days. The pulse rate remained above 135 per minute during this period. On the fourth day the hæmoglobin value was 18·9 grammes *per centum*, and the red blood cells numbered 6,500,000 per cubic millimetre; on the fifteenth day the figures were 15·6 grammes *per centum* and 5,100,000 per cubic millimetre respectively.

Immediately after the operation the cyanosis dramatically disappeared and the patient's colour became normal.

The patient made an excellent recovery, and after two and a half years he is well. There is no cyanosis; slight "clubbing" of the fingers and toes is present,

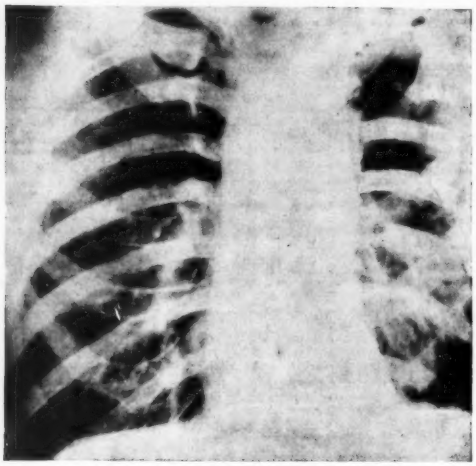

FIGURE IV.

Case I, 1951. Postero-anterior view of the chest three years after successful resection of upper lobe of the left lung.

but his chest is clear (Figure IV). Examination of his cardio-vascular system reveals no abnormality. This patient had no other evidence of arterio-venous shunts or of telangiectases. There was no family history of telangiectasia.

Three observations may be made from this case history. Firstly, it is similar to two others described, inasmuch as the patients had been under observation for fifteen years before diagnosis was made and surgical cure achieved. This is not surprising, since only some 40 cases have been described up to 1949. Erf (1949) described the history of a patient who had been in and out of hospital for fifteen years with a diagnosis of Ayerza's disease. His case was finally diagnosed, but the patient refused operation and died two years later from massive pulmonary hæmorrhage.

Brobeck (1948) reported the case of a patient followed from 1934 and examined every year up to 1947, when a correct diagnosis was made and successful cure was achieved by resection.

Forsee *et alii* (1950) quote the case of a young soldier who was treated in a sanatorium for three months before a correct diagnosis was made.

The second important observation is that the patient's polycythæmia was of such a severe grade that it was responsible for cerebral symptoms. About half the patients described in the literature showed cerebral symptoms such as dizzy spells, transient weakness or numbness, brief spells of inability to speak or attacks of unconsciousness or convulsions. These symptoms are probably the result of transient periods of increased cerebral anoxia associated with polycythæmia and lower hæmoglobin saturation. They disappeared after operation. In subjects coming to necropsy, no cerebral vascular lesions have been found.

Lastly, the bruit which is usually present in nearly two-thirds of the cases is usually systolic in time. It may be continuous, but it is often increased in intensity at the end of deep inspiration. The murmur must be recognized as being extra-cardiac and being usually associated with a heart which is normal in size and shape, and this fact differentiates the condition from congenital heart disease of the cyanotic type.

CASE II.—A young man, aged twenty years, was referred to us from the Tuberculosis Clinic. In 1945 he had coughed up blood and suffered from fits. His doctor had prescribed phenobarbitone tablets and vitamin *K*, which treatment he had continued up to 1949. During this time he had had at least three further attacks of hæmoptysis, but his fits had disappeared. They were considered to be typically epileptiform in character.

During 1949 he was investigated in the Tuberculosis Clinic, and although it was reported that numerous colonies of acid-fast and alcohol-fast bacilli were grown from his gastric contents, they did not produce tuberculosis in the guinea-pig. Finally it was considered that other causes than tuberculosis might be operative, and it was suggested that possibly an adenoma not visible in the bronchoscopic examination might be present, or even possibly bronchiectasis, although the symptoms were not very suggestive of this condition. On the other hand, it was thought that his symptoms might be due to chronic infection or to a vascular abnormality. These diagnoses were presented because there was a constant opaque area in the mid-zone of the right lung (Figure V).

On physical examination of the patient there were no outstanding abnormal features. He was not cyanosed; "clubbing" of the fingers and toes was just obvious. No telangiectases were found, although he had a pigmented area on his lower lip. His heart sounds were regular and closed, but a soft systolic murmur was heard in the third right intercostal space

about three centimetres from the right border of the sternum. The hæmoglobin value was 13·6 grammes *per centum*. The erythrocytes numbered 6,000,000 per cubic millimetre. A bronchogram of the right lung was normal in appearance, but it clearly delineated the segments and indicated that the opaque area in the right lung was in the posterior segment of the upper lobe close to the pulmonary artery. This opaque area appeared to be connected to the hilar region by a broad sinuous band.

Angiography displayed the vascular shadow early when the dye was in the right ventricle, and confirmed the diagnosis of arterio-venous fistula.

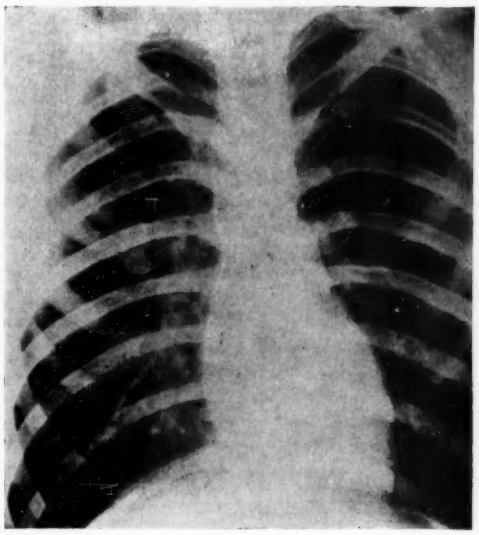

FIGURE V.

Case II, 1951. Postero-anterior view of the chest showing an opaque area in the posterior segment of the upper lobe of the right lung, close to the pulmonary artery and connected to the hilar region by a broad, sinuous band.

In accordance with the work of Lingren (1946) and of Ettinger, Magendantz and Russo (1949), radiographs were taken on full inspiration and on expiration. These showed that the lesion became smaller when the intrathoracic pressure was raised, and larger when it was decreased. Tomograms showed up the condition very clearly (Figure VI).

Radiographic examination of the skull revealed no abnormality.

It was noticed that, during the last six months, the patient's colour had appeared more suffused and his hæmoglobin value had increased to 17·8 grammes *per centum*, while the hæmatocrit value was 57; but, nevertheless, there was no obvious cyanosis when the patient stood alongside a man of similar build and age.

This, indeed, was an early case, but two important details had been missed in the history. It was discovered that the patient had suffered from epistaxis for years, and also that his mother had " blood-spots " on both hands, which bled at times, and it was found that she too suffered from nose bleeding.

Although the vascular shadow was not large, in view of the repeated hæmoptyses it was considered that early resection should be carried out.

Operation was performed on October 3, 1951, by Dr. F. J. Clark. There was no obvious vascular abnormality on macroscopic appearance of the right lung, but a purplish discoloration was found on the under-surface of the upper lobe towards the hilum. When this area was palpated, the tissues below it appeared softer than normal lung tissue. The upper lobe of the right lung was removed.

The patient made an uneventful recovery. Dissection of the specimen revealed a vascular sac measuring about two centimetres by one centimetre,

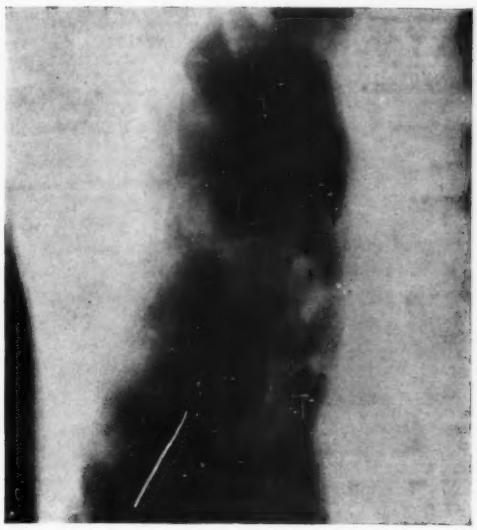

FIGURE VI.

Case II, 1951. The tomogram shows clearly the opaque area in the middle lobe of the right lung.

but unfortunately it had ruptured at operation. It was impossible to inject the branches of the pulmonary artery and the branches of the pulmonary vein, but dissection of the specimen revealed large vessels entering and leaving the sac.

This case illustrates two important points.

The familial nature of telangiectases has been well recognized, and this patient's mother had telangiectases of the hands and nose. The patient had telangiectases, presumably of the nose and the lung, the pulmonary lesion being the more conspicuous.

Pugsley and Janes (1951) state that small telangiectases of the skin and of the mucous membranes of the nose and oral cavity have been noted in 40% of the cases in which pulmonary lesions of like nature are present.

Hæmoptysis may be a salient symptom. This patient had five recurrences of hæmoptysis

Of the previous cases reported hæmoptyses occurred in one-quarter, and in a few instances were responsible for the death of the patient. The pulmonary lesion was not large, and therefore, the arterio-venous shunt was not great enough to produce obvious cyanosis, well - defined polycythæmia or severe " clubbing " of the fingers and toes.

CASE III.—In 1943 a boy, aged fourteen years, was admitted to the Royal Perth Hospital with a diagnosis of Ayerza's disease. At the age of nine years he had been sent to an orphanage as a neglected child, and at that time was considered to suffer from chronic heart trouble. He stated that at the age of twelve years he had coughed up two cupfuls of dark red blood with clots and was in hospital for two months.

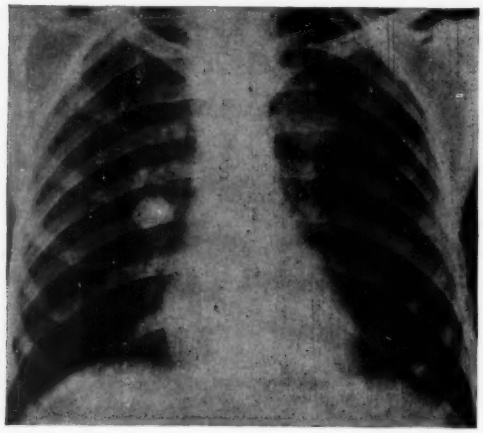

FIGURE VII.

Case III, 1943. Postero-anterior view of the chest, showing many shadows in a case of multiple pulmonary vascular shunts.

Physical examination showed the child to be cyanosed, with " clubbing " of the fingers and toes. He had a dry cough, but was not short of breath. His hæmoglobin value was 15·6 grammes per 100 millilitres; the erythrocytes numbered 5,400,000 per cubic millimetre.

The radiologist reported as follows (Figures VII and VIII):

> The cardiac outline is normal.
>
> The left lung showed a " fan-shaped " opacity commencing in the upper pole of the hilum and extending upwards into the upper zone.
>
> On the right side several rounded and well-defined opacities, varying in size from a pea to a walnut, were seen in the hilar and perihilar zone. It seems probable that these opacities are neoplastic in origin or else represent disease of the lymph glands or tuberculosis.

Examination with the use of lipiodol gave no further information.

This lad developed generalized peritonitis and died in a day or two. A necropsy showed that both lungs were slightly collapsed. There were livid dark blue lesions on the free surface of all lobes of the lungs except the middle lobe of the right lung. These lesions were situated at the apex, and the base of the left lung and on the lateral aspect of the right lung; all of them had the same appearance and consisted of dilated vessels, which showed direct communication with artery and vein. The saccular spaces were filled with dark venous blood. The walls of these cavities were not thickened. The rest of the lung tissue was normal.

The cause of death was generalized peritonitis, arising from a large abscess in the body of the pancreas. The head of the pancreas had disappeared and was substituted by a fibrotic mass.

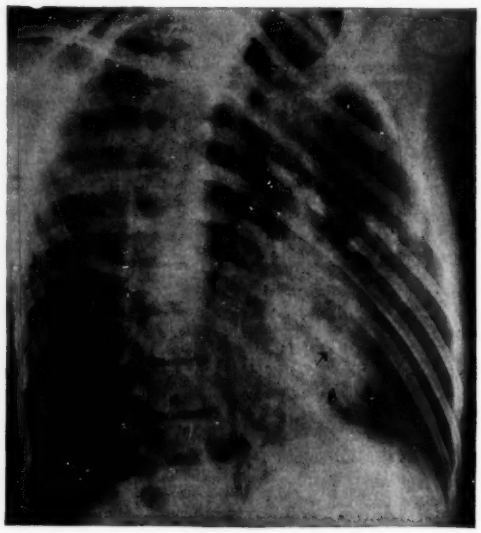

FIGURE VIII.

Case III, 1943. Lateral view of the chest, indicating the presence of several vascular opaque areas proved at post-mortem examination to be due to numerous telangiectases.

Microscopic examination revealed a direct communication existing between the branches of the pulmonary artery and the dilated veins forming an arterio-venous shunt. Microscopic examination of sections revealed grossly dilated veins surrounded by alveoli filled with blood. The alveolar capillaries were engorged and their walls thickened. There was also some fibrosis in the neighbourhood of the dilated veins. The alveolar hæmorrhages were considered to be terminal.

COMMENT

This was a case of multiple pulmonary telangiectases, which was not diagnosed until after death. With the increased recognition of this syndrome, there have already appeared reports of multiple local excisions with cure.

DISCUSSION

In the condition of pulmonary telengiectasia it is possible that the lesion may be recognized by the radiologist during routine radiographic

examination of the chest, or else the syndrome may be suspected when a young person, usually in the second or third decade, presents with progressive cyanosis, " clubbing " of the fingers and toes, severe secondary polycythæmia, transient dizzy spells and shortness of breath, without evidence of heart disease, but sometimes with a history of epistaxis and small telangiectases of the skin or mucous membranes.

The radiographic evidence of discrete densities in the lung, whether saccular, circoid or racemose, connected to the hilar region by broad sinuous bands, is suggestive evidence of a pulmonary arterio-venous shunt. The plain X-ray film is usually diagnostic.

Sometimes an extracardiac murmur is heard best in deep inspiration.

This arterio-venous shunt is simply a dilatation of the vessel between an artery and the corresponding vein. These dilated vessels, which are really a modified capillary, artery and vein, constitute a telangiectasis.

As the arterio-venous communication enlarges, the afferent vessel and the efferent vein dilate and become tortuous. The artery becomes thin-walled in its dilated part; the result is a cavernous telangiectasis—it is not a tumour.

It is considered that this is a more correct terminology than the terms arterio-venous fistula or cavernous hæmangioma.

The most confusing conditions are usually pulmonary tuberculosis, congenital heart disease of the cyanotic type, bronchiectasis, *polycythæmia rubra* and tumours of the lung.

Once the diagnosis has been made, the dangers which are most common and which must necessitate early operation, are the risk of fatal hæmorrhage, phlebothrombosis, pulmonary embolism, subacute bacterial endocarditis, syncopal attacks and the progressive nature of the lesion, together with the resulting psychological stress on the patient once the diagnosis has been made.

Surgical excision of the pulmonary lesion or lesions (as sometimes they are multiple) offers the only means of cure.

SUMMARY

1. A classification of vascular abnormalities of the lung is outlined.

2. Various pathological states resulting from these anomalies are recorded.

3. The importance to the surgeon of the recognition of abnormal vascular connexions is stressed.

4. The clinical syndrome of pulmonary telangectasia is illustrated by three case reports, and support is given to the use of the term pulmonary telangiectasis rather than to arterio-venous aneurysm or arterio-venous fistula.

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REFERENCES

ALLANBY, K. D., BRINTON, W. D., CAMPBELL, M., and GARDNER, F. (1950), " Pulmonary Atresia and the Collateral Circulation to the Lungs ", *Guy's Hosp. Rep.*, **99**, 110.

BRANTIGAN, O. C. (1947), " Anomalies of the Pulmonary Veins ", *Surg. Gynec. and Obst.*, **84**, 653.

BRINK, A. J. (1950), " Telangiectasis of the Lungs with Two Case Reports of Hereditary Hæmorrhagic Telangiectasis with Cyanosis ", *Quart. J. Med.*, **19**, 239.

BRINTON, W. D. (1950), " Primary Pulmonary Hypertension ", *Brit. Heart J.*, **12**, 305.

BROBECK, OLAF (1948), " A Case of Arteriovenous Aneurysm of the Lung Cured by Resection ", *Acta Cardiol.*, **30**, 371.

BRUWER, A., CLAGETT, O. T., and MCDONALD, J. R. (1950), " Anomalous Arteries of the Lung Associated with Congenital Pulmonary Abnormality ", *J. Thoracic Surg.*, **19**, 955.

BURCHELL, H. B., and CLAGETT, O. T. (1947), " The Clinical Syndrome Associated with Pulmonary Arterio-Venous Fistulas Including a Case Report of a Surgical Cure ", *Am. Heart J.*, **34**, 151.

DETERLING, R. A., and CLAGETT, O. T. (1947), " Aneurysm of the Pulmonary Artery. Review of the Literature and Report of a Case ", *Am. Heart J.*, **34**, 471.

ERF, L. A. (1949), " Pulmonary Hæmangioma ", *Am. Heart J.*, **38**, 766.

ETTINGER, A., MAGENDANTZ, H., and RUSSO, E. A. (1949), " Arteriovenous Aneurysm of the Lung ", *Radiology*, **53**, 261.

EVANS, W. (1951), " Pulmonary Hypertension ", *Proc. Roy. Soc. of Med.*, **44**, 600.

FORSEE, J. H., MAHON, H. W., and JAMES, L. A. (1950), " Cavernous Hæmangiona of the Lung ", *Ann. Surg.* **131**, 418.

HARRIS, H. A., and LEWIS, I. (1940), " Anomalies of the Lungs with Special Reference to the Danger of Abnormal Vessels in Lobectomy ", *J. Thoracic Surg.*, **9**, 666.

HAYWARD, J., and REID, L. (1949), " Pulmonary Telangiectasis ", *Thorax*, **4**, 137.

LENDRUM, A. C., SCOTT, L. D. W., and PARV, S. D. S. (1950), " Pulmonary Changes Due to Cardiac Disease ", *Quart. J. Med.* (New Series), **19**, 249.

LILLIAN, M. (1949), " Pulmonary Artery Aneurysm ", *Am. J. Med.*, **7**, 280.

LINGREN, E. (1946), " Roentgen Diagnosis of Arteriovenous Aneurysm of the Lung ", *Acta Radiol.*, **27**, 585.

MARCHAND, P., GILROY, J. C., and WILSON, V. H. (1950), " An Anatomical Study of the Bronchial Vascular System and its Variations in Disease ", *Thorax*, **5**, 207.

PRINZMETAL, M., ORNITZ, E. M., SIMKIN, B., and BERGMAN, H. C. (1948), " Arterial Venous Anastomoses in Liver, Spleen and Lungs ", *Am. J. Physiol.*, **152**, 48.

PRYCE, D. M. (1946), " Lower Accessory Pulmonary Artery with Intralobar Sequestration of Lung. A Report of Seven Cases ", *J. Path. and Bact.*, **51**, 457.

PUGSLEY, H. E., and JANES, R. M. (1951), " Arteriovenous Aneurysm of the Lung ", *Dis. Chest*, **20**, 177.

SABIN, F. R. (1922), " Origin and Development of the Primitive Vessels of the Chest and of the Pig ", *Contrib. Embryol.* (Carnegie Inst.), **14**, 139.

SUTHERLAND, H. D'ARCY (1950), " Intralobar Sequestration of Lung Associated with an Abnormal Pulmonary Artery ", *Clinical Reports of the Adelaide Children's Hospital*, **1**, 1.

THOMPSON, W., and SHAFER, J. C. (1951), " Congenital Vascular Anomalies ", *J.A.M.A.*, **145**, 869.

TOBIN, C. E., and ZARIQUIEY, M. O. (1950), " Arteriovenous Shunts in the Human Lung ", *Proc. Soc. Exper. Biol. and Med.*, **75**, 827.

WHITAKER, W. (1947), " Cavernous Hæmangiomata of the Lungs ", *Thorax*, **2**, 58.

WOOD, D. A., and MILLER, M. (1938), " Role of Dual Pulmonary Circulation. Various Pathological Conditions of the Lungs ", *J. Thoracic Surg.*, **7**, 649.

CONTROL OF THE WATER CONTENT OF THE BODY

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In 1916 Henderson stated that "the regulation of volume (in biology) has remained without any physico-chemical analysis. Yet from the standpoint of physical science, this is perhaps the most universal and fundamental of all organic regulations." Since then the mechanisms which give rise to œdema have for many years been the subject of a large amount of physiological investigation. The fact that excess fluid retention in the body is nearly always accompanied by a commensurate electrolyte retention has in recent years focussed attention on the mechanism controlling electrolyte excretion from the body. The observation that variations in the behaviour of electrolyte content occur in œdema states does not, however, mean that these variations have produced the œdema. They can be explained just as satisfactorily as secondary adjustments necessitated by the accumulation of water within the body.

The concept that œdema is due primarily to an upset of volume regulation has been put forward by several authors in the past, and in this paper it is proposed to examine this concept in the light of observations made during the past three years in the Clinical Research Unit of the Alfred Hospital.

In 1925 McLean commented, "that there is a steady state in volume relations in the organism is manifested in the fact that the total bodily volume and the internal distribution of bodily fluids both show an apparent stability, in spite of continual interchange of fluids between the infinite assemblage of phases which make up the organism". This steady state is evidenced by the fact that most individuals maintain their body weight within narrow limits over long periods despite marked variation in fluid intake. Further, the water content of various tissues has been shown to be a constant proportion of this weight (Adolph, 1921).

[1] Part of the expenses of this investigation were defrayed by a grant from National Health and Medical Research Council.

The water content of the body can be divided into two major parts: (*a*) that within the cells (intracellular), and (*b*) that in the tissue spaces and channels (extracellular).

The water of the intracellular space is present both as solvent for intracellular materials and as an integral part of the protoplasm. Only relatively small changes in the quantity present as a solvent within the cell are compatible with life, and marked changes in the quantity present as an integral part of the protoplasm imply marked changes in the mass of cells in the body. Therefore, if the mass of cells within the body is relatively constant, only minor changes will occur in the total quantity of intracellular water within the body. It is probably correct therefore to say that the quantity of intracellular fluid is largely determined by the metabolic activities of the cells. Intracellular water represents some 50% of the total body weight amounting to some 35 litres in a 70 kilogram person. In a series of patients with œdema from cardiac failure studied by Millar (1951), the maximum increase in intracellular volume recorded was about 25% of the individual's normal volume; in most cases, however, it was of the order of 10% and frequently there was no change, even in the presence of gross œdema.

The water of the extracellular space is divided between the interstitial and plasma fluids in the ratio of approximately 4 : 1, and represents some 20% of the total body weight representing some 14 litres in a 70 kilogram person. Its function appears to be that of a vehicle for transport of metabolites and other substances and great changes in its volume are seen in abnormal states. We have observed in one case of œdema an increase of two and a half times in the volume of extracellular fluid as measured by the chloride space and increases of 100% are common. It is seen, therefore, that in œdema states the major change in volume occurs in the extracellular compartment.

When excess of fluid (œdema) is present in the body this contains electrolytes in much the same concentrations as those existing in the normal fluids. This implies that there has been

retention of electrolytes *pari passu* with the retention of fluid, and furthermore that the mechanisms of the body which control the electrolyte content of body fluids are functioning substantially in a normal fashion.

In this connexion it is pertinent to note that normally a steady state in relation to electrolytes must also exist, for there is a continuous intake and output of electrolytes. This steady state has been analysed in some detail by both Wolf (1945) and Wesson (1948) and their co-workers, and Wesson points out with reference to sodium that such " a steady state cannot be achieved by the progressive, uniform excretion of excess sodium in accordance with renal clearance principles since an infinite time would be required to reach equilibrium. This difficulty seems to be resolved, as in other physiological systems, by overcompensation and hence oscillation about the steady state as a mean."

Although in general retention of water is associated with retention of electrolytes, the concentration of electrolytes or osmotic pressure of the fluids can play no part in the regulation of the volume of the solvent, because any given concentration of electrolytes or osmotic pressure can be obtained in any given volume of solvent if the correct amount of solute is present. Further, although it is established that retention of sodium in man leads to water retention, there is no conclusive evidence that water retention always leads to sodium retention, although frequently this is so (Smith, 1951).

It seems likely, therefore, that the control of body water volume is independent of electrolyte control, and some mechanism which is sensitive to body volume and which controls the water balance must be postulated, even if its afferent and efferent pathways are unknown. The existence of such a mechanism, sited in the mid-brain, was postulated by Molitor and Pick (1923), although this work was subsequently questioned by Theobald (1934). More recently a similar mechanism has been suggested by Viar *et alii* (1951) after they studied the effect of posture and of compression of neck veins on renal excretion of water and sodium.

If there is a volume-regulating mechanism, then œdema may be considered as a quantitative disturbance of volume regulation ; an unbalance between volume-disturbing and volume-restoring forces (McLean, 1925).

All the component parts of this system are not known, but the circulatory system, endocrine glands and kidney must be some of them. Frequently gross disturbances of function in these components occurs without resultant œdema or dehydration and so within wide limits the volume-regulating mechanism must be able to compensate for defects in its component parts. The production of œdema must then represent either disturbances of some component part of the system which are beyond the range of compensation or disturbance of the control itself.

Of the component parts of the system the circulatory mechanism, the kidney and ductless glands have been studied in detail, and Wesson *et alii* (1948) suggest that linking together of the renal control of sodium excretion, pituitary control of water excretion and glomerular control of filtration rate would give an integrated system which could regulate the composition and volume of extracellular fluid. However, the means by which these organs are appraised of the needs for adjustment of body fluids are not clear. Moreover, the excretion of water and the excretion of solute condition one another (Elkington, 1950).

Although in œdema the dominant change is in the extracellular fluid content, some changes do occur in the intracellular water content. Seldin and Tarail (1949) have produced evidence that the state of hydration of body cells has some influence on the excretion of sodium, by affecting the partition of ingested sodium between intracellular and extracellular fluid.

OBSERVATIONS ON PATIENTS WITH ŒDEMA

During the past three years in the Clinical Research Unit a detailed study has been made of the way in which œdematous patients lose their excess water.

This has been done by accurate daily weighing of the patient and careful recording of daily water balance, whilst the patient has been on a known regimen of fluid intake, sodium intake, caloric intake and stated drug therapy. The records of daily weight and water balance were recorded in graphic form (Figure 1).

In a previous paper (Lowe 1951) it was shown that patients with œdema from congestive cardiac failure treated by the above regimen show, in most instances, a uniform behaviour. The dominant feature of this behaviour is a loss of water which is constantly changing but in accord with an underlying definite cyclic pattern. The fluid loss commences slowly and then accelerates for several days, after which it diminishes until a balance state is reached. After this point there follows short periods of increasing and decreasing fluid retention and a further period of fluid loss. In other words after initially reaching a balance at the correct body volume, the system oscillates to rest.

Occasionally in some patients this whole change is preceded by a short period of diminishing fluid retention before the diuresis commences. This behaviour is illustrated in Figure I, in which the cyclic nature of the fluid loss is evident in the water balance curves, integration of which gives a weight curve that agrees well with the observed weights.

Repeated observations on the same patient show that this behaviour is reproducible.

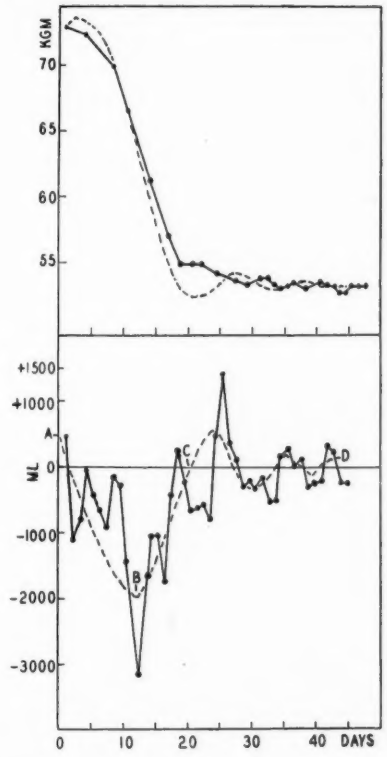

FIGURE I.

Weight (upper) and water-balance (lower) curves during diuresis in a case of congestive cardiac failure. Solid lines join observed values. The broken lines represent the hypothetical smoothed water-balance curve and the corresponding weight curve. The letters A, B, C, D indicate the portions of the water-balance curve referred to in Table I.

This same phenomenon of cyclic water loss has also been observed in patients œdematous from acute nephritis. Figure II shows the weight and water balance curves from such a patient and it is apparent that they are similar to those of Figure I.

The use of certain organic mercury compounds as diuretics in the treatment of œdema is well established, and in most cases they produce a rapid loss of the excess water from the body. However, study of patients treated with these compounds along the lines indicated shows that the same underlying rhythmic water loss is present. To some extent the effect of the mercurial diuretic depends upon the quantity of excess water present in the body. Figure III shows the effect of repeated injections of a mercurial diuretic in a very œdematous patient. The smooth cyclic curve of water loss is apparently not disturbed, except that its period is probably shortened. However, when the patient's body water has reached its normal volume, it is noted that the smooth curve disappears and there are sudden losses of water after the injection of mercury followed by fluid retention until the next injection.

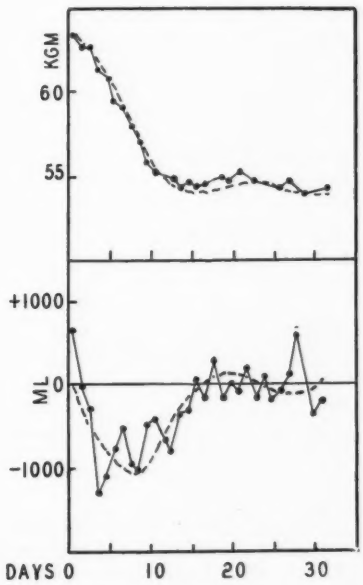

FIGURE II.

Weight (upper) and water-balance (lower) curves during diuresis in a case of acute nephritis. The solid and broken lines as in Figure I.

It was noted by Borst (1950) that, during fever, diuresis is inhibited and in one of the cases previously recorded (Lowe, 1951) it was shown that fever temporarily inhibited the diuretic cycle.

These observations indicate, therefore, that a uniform behaviour of the changes in body volume can be discerned in œdematous patients during fluid loss. Further this behaviour is seen in at least two œdematous conditions—congestive cardiac failure and acute nephritis—

and it is disturbed but not fundamentally altered by mercurial diuretics. It is inhibited by some febrile states.

This evidence, taken together with that quoted from the literature, indicates that the cyclic curves noted probably describe some facet of the behaviour of the unknown body volume regulator. This undefined mechanism is apparently slow-acting, taking many days for each cycle, and it appears to oscillate towards a balance state at normal body water volume.

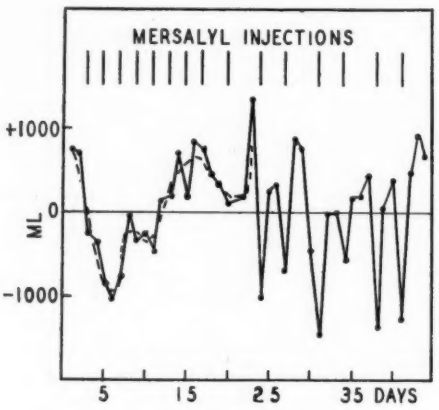

FIGURE III.

The water-balance curves during diuresis in a case of congestive cardiac failure treated with mersalyl injections as indicated. Solid and broken lines as in Figure I.

If these curves do describe some aspect of the behaviour of the volume-controlling mechanism then an analysis of them may give clues as to other features of the system. Even though the shapes of the curves vary from patient to patient, they all belong to one mathematical family. This cyclic characteristic is evidence of a dynamic equilibrium within the body and indicates that the problem of the control of body water content may be viewed as another of the numerous already recognized biological rhythms and cycles (Kleitman, 1949).

THE BODY AS AN "OPEN" STORAGE SYSTEM FOR WATER

Comparison with the obvious analogue, that of hydraulic flow through a storage system such as a reservoir, which may be considered as an "open" system, suggests that the process of bodily storage of water may be similarly studied. In this section water storage in the body is analysed in terms of an "open" system.

An "open" system is one which has contact with its surroundings in such a manner that there is transfer of material (either common or various) and energy between the system and its surroundings. That is, balance states are the result of dynamic equilibria.

The following general equation (1) is available for "open" systems of this type:

$$\text{Input} = \text{Output} + \text{storage increase.} \qquad (1)$$

In the case of the human body the input in any given time is represented by the sum of the water drunk, the water content of the food eaten, and the water produced by metabolism. Although two of these components enter the alimentary canal intermittently, it has been assumed that, in these observations, the rate at which fluid enters the extracellular fluid compartment is approximately constant. The output is represented by the sum of the volume of urine passed and the water lost by evaporation from the skin and the lungs, and the water content of the fæces. Of these losses it was considered that only urine loss was variable under the conditions of observation and the loss by other routes was corrected for in construction of the curves (Lowe, 1951). The storage change was considered to be represented by the change in weight of the body and is thought to be essentially the change in volume of the extracellular space, and is represented by the curves illustrated.

The formal equation (2) corresponding to the "open" storage system may be written (Stevens, 1921)

$$\frac{dy}{dt} + \frac{y(t)}{h(t)} = \frac{x(t)}{h(t)} \qquad (2)$$

where $y(t)$ is the output,

$x(t)$ is the input,

$h(t)$ is the instantaneous value of the slope of the output-storage curve; this curve is characteristic of the particular system under study.

The first term in this expression represents the time rate of change of the output, the other two terms are quotients.

As the water balance curves (Figures I, II and III) may be considered to represent water output curves (see equation 4 below), they represent the function $y(t)$ and as such should be solutions of equation (2). To this end the following investigation of the form of these curves was made.

The descriptive formula (3) has been found to represent the curves of a number of cases of œdema studied during the recovery phase

$$y = e^{at+b} \cos (e^{ct+d} + f) \qquad (3)$$

where y is the fluid balance amplitude at time t.

a, b, c, d and f are constants which may move over restricted ranges from case to case and from section to section of any one case (see Table I). e is the base of the natural logarithm. As e^{ct} is a non-linear function of time, the period of the curve oscillations will vary in a continuous and non-linear manner. If a is non-zero, the amplitude term will vary with time, and consequently the amplitude of the oscillations will vary with time. The factor f is a phase factor determined by the starting phase of the various segments of the oscillation.

TABLE I
Constant Ranges

Constant.	Range. (Five Cases.)		Figure I.		
			Between A and B.	Between B and C.	Between C and D.
a	−0·002	+0·029	−0·025	−0·066	−0·066
b	+1·365	+3·357	+2·277	+3·355	+3·357
c	+0·003	+0·054	+0·046	+0·048	+0·054
d	+0·559	+4·678	+0·559	+0·692	+0·877
f	−48·73	−0·85	−2·38	−0·848	−1·366

By substitution of expression (3) into equation (2), it can be confirmed that (3) does satisfy the equation and hence that the form of the output curve is compatible with an " open " storage system of the type suggested.

As it appears that equation (2) is applicable to the storage of water in man, the form of the storage controlling function of time $h(t)$ has been investigated, since this function defines the characteristics of the system.

Referring back to equation (2), it will be seen that the balance curve is simply the curve of the output $[y(t)]$ with a shifted baseline. For if the input $[x(t)]$ is assumed constant, as in our experiments, the balance curve which gives the values of

$$\text{output} - \text{input} = y(t) - x(t) = y(t) + k \qquad (4)$$

where k=a constant

From the above formulæ (2) (3) the function $h(t)$ may be determined, either analytically (equation 5) or graphically. A graphical solution has been made for one case (Figure IV), which is a typical case leading to a typical result. These curves for values of $h(t)$ are not dissimilar to cotangent curves. Alternatively, substitution of expression (3) in equation (2) and solution of the latter for $h(t)$ leads to the following result (equation 5):

$$h(t) = \frac{1}{a - c.e^{(ct+d)} \tan \alpha} \qquad (5)$$

where $\alpha = e^{(ct+d)} + f$.

As will be seen in Table I, in all of our cases a is small, hence the function $h(t)$ shows a form not dissimilar to a cotangent curve (compare with graphic solution).

On the basis of these curves one may visualize two separate control processes in action. The first determines the general form of the continuous section of the $h(t)$ curve. The second alters the instantaneous slope of the curve for all finite points from one periodicity to the next, as evidenced by the changing slope of successive branches of $h(t)$ near, but not at the zero-axis. This latter process virtually alters the sensitivity of the output-storage mechanism from cycle to cycle of the output. It becomes more sensitive as the patient approaches normal weight.

Consider the first process. The peculiar nature of the $h(t)$ curve suggests that two antagonistic control factors are concerned in the

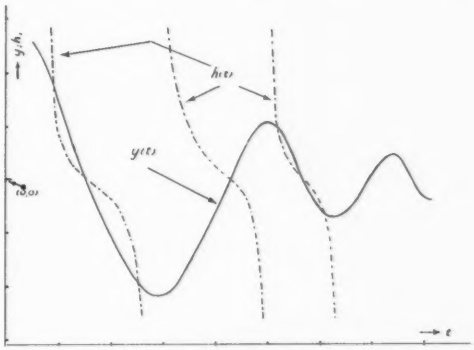

FIGURE IV.
Output curve $[y(t)]$ corresponding to the balance curve of Figure I and the $h(t)$ curves graphically derived from it (see text).

first process, and it seems possible that clearly defined regions of single control by one or other of the factors may be present. At one end of each branch one only of the factors may be in control, and *vice versa*. In the central, " through-zero-going ", region, control may be shared.

It should be made clear at this stage that while the calculation of the output-storage slope function $h(t)$ has proceeded from the output curve and a defined input curve, the function $h(t)$ is a fundamental property of the system and $y(t)$ is a result of a given form of $h(t)$. Thus from a consideration of $h(t)$ it is possible to arrive at an understanding of $y(t)$. Furthermore, examination of other balance curves demonstrates that similar $h(t)$ curves exist in other cases, so the present case may be considered typical.

Observation of the relative location of the poles of the function $h(t)$ and the resultant movement of $y(t)$ suggests that of the two factors one tends to restore the body fluid

volume to some standard value, that is to say, to reduce the rate of change, whilst the other factor tends to swing the body fluid volume away by disturbing the instantaneous water balance. This concept of the antagonistic volume-restoring and volume-disturbing factors is a straightforward deduction from the starting point which assumed the process of water storage in the body to have the characteristics of an " open " storage system.

Study of the second process, which appears to control the sensitivity of the output-storage mechanism, has not been developed so far. Now since $h(t)$ is the slope of the storage-outflow curve, a larger value of $h(t)$ for a given phase in one branch than for $h(t)$ at the same phase in a preceding branch indicates a rising sensitivity of the storage-outflow mechanism. Apart from regions near the poles, a large slope of $h(t)$ means that only a small change in storage is necessary to result in a rapid output change; that is, a high correction speed becomes associated with a small change in storage and in storage rate of change. This is demonstrated by the smaller amplitude and shorter period of the later oscillations compared with the earlier. The maintenance mechanism is, at later stages, operating at a much higher sensitivity and is able to clear excess fluid from the body rapidly.

If the previous considerations are admitted, examination of both control processes together leads to the unavoidable conclusion that the first process (of antagonistic factors) is probably operating normally in these œdema states. Apparently the mechanism which is not functioning in a normal manner is the second process (control of the sensitivity of the storage regulatory mechanism).

This analysis of the curves demonstrates, first, that the equation (2) for an " open " storage system may be employed to determine the characteristic output-storage slope relation for each case studied.

Secondly, it indicates the presence of two separate processes controlling body water content. One of these processes appears to contain two antagonistic factors, one restoring and the other disturbing the total body water content. The other process appears to contain a factor which alters the sensitivity of the output-storage relation.

CONCLUSIONS

Our observations on the process by which water is lost by œdematous patients during diuresis indicate the existence of a volume-controlling mechanism within the body which causes the body water volume to return to normal in an oscillatory manner. This is in accord with the prediction made by Wesson *et alii* (1948) in their studies on sodium excretion. Such an oscillatory phenomenon is, of course, common in biology.

Analysis of the curves of water balance reveals that the volume-controlling mechanism has several discernible features. First, there exist volume-disturbing and volume-restoring forces as postulated by McLean (1925). Secondly, it appears that the sensitivity of this mechanism changes from time to time, becoming more sensitive as normality is approached. It is possible that sensitivity changes in this mechanism may be one of the factors leading to the development of, and recovery from, œdematous states.

SUMMARY

The evidence for a water volume controlling mechanism in man is examined in the light of clinical observations on patients with œdema.

It is concluded that such a mechanism exists and that as components there are volume-disturbing and volume-restoring forces, and that the sensitivity of this mechanism is altered in œdematous states.

ACKNOWLEDGEMENTS

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REFERENCES

ADOLPH, E. F. (1921), " The Regulation of the Water Content of the Human Organism ", *J. Physiol.*, **55**, 114.

BORST, J. G. G., and DE VRIES, L. A. (1950), " The Three Types of ' Natural ' Diuresis ", *Lancet*, **2**, 1.

ELKINGTON, J. R. (1950), " Water Metabolism ", *Ann. Rev. Physiol.*, **12**, 145.

HENDERSON, L. J. (1916), " On Volume in Biology ", *Proc. Nat. Acad. Sci.*, **2**, 654.

KLEITMAN, N. (1949), " Biological Rhythms and Cycles ", *Physiol. Rev.*, **29**, 1.

LOWE, T. E. (1951), " Fluid Balance in Congestive Cardiac Failure: Two Mechanisms in Diuresis ", *Lancet*, **2**, 851.

MCLEAN, F. C. (1925), " Edema as a Physiological Regulation ", *Physiol. Rev.*, **5**, 618.

MILLAR, G. E. (1951), " Water and Electrolyte Metabolism in Congestive Heart Failure ", *Circulation*, **4**, 270.

MOLITOR, H., and PICK, E. P. (1923), quoted by Theobald, G. W. (*loco citato*).

PETERS, J. P. (1935), "Body Water", Thomas, Springfield, Illinois.

SELDIN, D. W., and TARAIL, R. (1949), "The Effect of Hypertonic Solutions on Metabolism and Excretion of Electrolytes", *Am. J. Physiol.*, **159**, 160.

SMITH, H. (1951), "The Kidney", Oxford University Press, New York, 337.

STEVENS, J. C. (1921), "Computing Reservoir Outflow and Height from Inflow and Capacity", *Engineering News Record*, **87**, 1031.

THEOBALD, G. W. (1934), "The Repetition of Certain Experiments on which Molitor and Pick Base their Water-centre Hypothesis and the Effect of Afferent Nerve Stimuli on Water Diuresis", *J. Physiol.*, **81**, 243.

VIAR, W. N., OLIVER, B. B., EISENBERG, S., LOMBARDO, T. A., WILLIS, K., and HARRISON, T. R. (1951), "The Effect of Posture and of Compression of the Neck on Excretion of Electrolytes and Glomerular Filtration", *Circulation*, **3**, 105.

WESSON, L. G., ANSLOW, W. P., Junior, and SMITH, H. W. (1948), "The Excretion of Strong Electrolytes", *Bull. New York Acad. Med.*, **24**, 586.

WOLF, A. V. (1945), "The Dehydrating Effect of Continuously Administered Water", *Am. J. Physiol.*, **143**, 567.

THE MALABSORPTION SYNDROME[1]

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The clinical association of symptoms of steatorrhœa, wasting, tetany and anæmia has come to be known as the "sprue syndrome". Sprue itself is a disease of unknown ætiology, possibly infective (Leishman, 1945; Woodruff, 1949), affecting European residents of tropical areas, which has been most carefully studied in all its aspects by Fairley (1930). The tetrad of symptoms also characterizes cœliac disease of infancy (Gee, 1888; Herter, 1908). Non-tropical sprue, or idiopathic steatorrhœa, is thought to be an adult form of cœliac disease, an inherited jejuno-ileal insufficiency (Bennet, Hunter and Vaughan, 1932; Thaysen, 1935; Snell, 1939). Symptoms may develop *ab initio* in adulthood or may have been present since childhood, causing some degree of infantilism.

A syndrome clinically indistinguishable from sprue may occur in some pathological conditions of the bowel and mesentery in which absorption of fat is defective: for example, chronic tuberculosis of the mesenteric lymph nodes (Hurst, Wright and Ryle, 1942; Mendez-Ferriera and Bargen, 1937), gastro-jejuno-colic fistula (Fairley and Kilner, 1931), lymph-adenoma and related conditions (Fairley and Mackie, 1937), ulcerous jejuno-ileitis (Crohn's disease) (Nyman, 1949). Whipple in 1907 described a case of steatorrhœa in which the mesenteric and intestinal lymph nodes contained large globules of fat and crystals of fatty acid, which he called intestinal lipodystrophy, and a few similar cases have subsequently been reported (Amsterdam and Grayzel, 1945).

The sprue syndrome therefore may be tropical or non-tropical, may occur in adulthood or infancy, and may be idiopathic or secondary to underlying abdominal pathology. There is abundant evidence that most of the clinical and biochemical features of the syndrome are due to defective absorption of fat, carbohydrate, vitamins and certain hæmatinic principles from the small intestine, and it has recently become clear that patients may present with incomplete clinical manifestations—for example, megaloblastic anæmia without steatorrhœa or tetany—to whom it would be inaccurate to apply the term sprue syndrome, since the clinical picture may not be in the least like sprue. A more comprehensive term which we prefer to employ is, following Davidson, the "malabsorption syndrome" which has the advantage of explicitly nominating a physiological anomaly.

The purpose of this communication is to draw attention to the multiplicity of clinical manifestations of the malabsorption syndrome, to discuss problems in differential diagnosis and to describe the relatively simple biochemical techniques which may be employed in the study of this syndrome.

Material and Methods

Four patients have been selected for discussion. In Cases I and II, malabsorption appeared to be an idiopathic defect, while in Cases III and IV malabsorption occurred secondary to disease of the intestine or mesenteric lymph nodes.

The following investigations were carried out in nearly all patients.

1. *Biochemical Tests of Intestinal Absorption.* (*a*) *Glucose.* Standard oral glucose tolerance test. (*b*) *Protein.* The oral glycine test described by Anfanger and Heavenrich (1949) was used. This test consists of the oral administration of 50 grammes of glycine, followed by the determination of α-amino nitrogen in the blood for five hours. Normal patients show a rise of at least 3·0 milligrammes *per centum* in the amino nitrogen after one or two hours. (*c*) *Fat.* A butter fat tolerance test was employed. Fifty grammes of butter are given orally, followed by the turbidimetric estimation of total serum lipides (Kunkel, *et alii*, 1948) for a period of five or six hours.

2. *Tests of Liver Function.* The quantitative van den Bergh estimation and cephalin flocculation test of Hangar were carried out; the total serum protein, the albumin-globulin ratio (modified Biuret method), the serum alkaline phosphatase content (method of King

[1] Aided by a grant from the National Health and Medical Research Council of Australia.

and Armstrong), and the prothrombin time (method of Quick as modified by Kark and Lozner, 1939) were estimated.

3. *Gastric Secretion.* The standard fractional histamine test meal was used.

4. *Gastric Biopsy.* In three patients the histology of the gastric mucosa was studied by the method of obtaining gastric biopsy material described by Wood *et alii* (1949).

5. *Other Biochemical Investigations.* The serum calcium content and the fæcal fat content were estimated.

TABLE I.

Biochemical and Hæmatological Findings in Four Patients with the Malabsorption Syndrome.

Observation.	Case 1. Idiopathic Malabsorption Syndrome.	Case 2. Idiopathic Malabsorption Syndrome.	Case 3. Gastro-Colic Fistula.	Case 4. Mesenteric Hodgkin's Disease.
Serum bilirubin (normal, 0·2 to 1·0 unit)	0·5	0·3	1·0	2·0
Cephalin flocculation (normal, 0)	+	0	0	0
Total serum protein (normal, 6·0 to 8·5 gms. *per centum*)	5·0	4·7	4·3	3·5
Serum albumin (normal, 3·5 to 5·2 gms. *per centum*)	3·9	2·3	2·6	1·5
Serum globulin (normal, 2·0 to 3·5 gms. *per centum*)	1·1	2·4	1·7	2·0
Alkaline phosphatase (normal, 3 to 13 K.A. units)	4	7	8	20
Prothrombin index (normal, 100%)	51	95	50	85
Serum calcium (normal, 9 to 11 mgms. *per centum*)	6·3	4·0	—	7·4
Blood urea (normal, 20 to 40 mgms. *per centum*)	23	54	42	53
Histamine test meal (normal, 40 to 60 units HCl)	6	63	33	No free HCl. 50 units total acid
Fæcal fat, dry weight	<30%	—	45%	35%
Gastric biopsy	Normal mucosa	Normal mucosa	—	Atrophic gastritis (after nitrogen mustard)
Hæmatology	Hb., 12·5 gms. *per centum* R.B.C., 3,310,000 C.I., 1·28 W.B.C., 2,500	Hb., 4·2 gms. *per centum* R.B.C., 1,300,000 C.I., 1·15 W.B.C., 1,300 Marrow, megaloblastic	Hb., 11·5 gms. *per centum* R.B.C., 4,030,000 C.I., 0·97 W.B.C., 11,400	Hb., 11·1 gms. *per centum* R.B.C., 4,200,000 C.I., 0·89 W.B.C., 6,000

CASE RECORDS

CASE I.—A male, aged fifty-three years, was admitted to hospital on May 1, 1950. He had served in the first World War, contracting dysentery in the Middle East in 1917. Since 1920 he had had short bouts of diarrhœa every two years, passing several fluid motions daily. Since 1946 he had complained of dyspepsia, poor appetite with intolerance to fat and the loss of two stone in weight. Soreness of the tongue was relieved by occasional injections of liver extract. Diarrhœa had become persistent and the motions were described as frothy and having an offensive odour.

Examination revealed a tall thin sallow man with excessive brown pigmentation of face and hands. His tongue was red and atrophic. His lungs, heart, abdomen and central nervous system were clear. The blood pressure was 108 millimetres of mercury, systolic, and 66 diastolic.

Investigation showed the chest to be clear on X-ray examination. The fæces macroscopically were pale and bulky; microscopically, abundant fat droplets and fatty acid crystals were seen. The hæmoglobin value was 12·5 grammes *per centum*. The red cell count was 3,310,000 cells per cubic millimetre. The colour index was 1·28. The white cell count was 2,500 cells per cubic millimetre. The hæmatocrit reading was 36%. Mean corpuscular volume was 109 cubic micromillimetres. Mean corpuscular hæmoglobin value was 31·4 micromicrogrammes. Mean corpuscular hæmoglobin concentration was 28·7%. Marked anisocytosis was present. The histamine test meal revealed 40 units of free hydrochloric acid. The biochemical findings (Table I) included hypoproteinæmia, hypocalcæmia and hypoprothrombinæmia. The thiamine excretion (24 hours) on admission was nil. Absorption tests (Figures V, VI, VII and VIII) revealed flat glucose and fat tolerance curves.

Treatment and Progress. He was treated with a diet with a high protein-low fat content and with vitamin supplements, and was given 80 microgrammes of vitamin *B*12 intramuscularly at first, followed by 40 microgrammes at weekly intervals. His diarrhœa rapidly became less and he gained weight. He was discharged from hospital on May 25, 1950. Although no reticulocyte response was observed following the initiation of vitamin *B*12 therapy, an improvement of the blood picture was subsequently noted. In November 1950 findings were: hæmoglobin value,

13·7 grammes *per centum*; red cell count, 4,950,000 cells per cubic millimetre; colour index, 0·94; white cell count, 9,000 cells per cubic millimetre.

This was a typical case of idiopathic steatorrhœa unrecognized for thirty years, with moderate macrocytic anæmia. Satisfactory remission of symptoms was obtained with diet and vitamin *B*12.

CASE II.—A female patient, aged forty-four years, was first admitted to hospital on January 14, 1948. For five years she had complained of mild dyspepsia and for two years had been troubled with prolapsing piles which occasionally bled. Four months before admission she developed severe diarrhœa, passing every day a dozen liquid motions, often blood-stained. She had become progressively pale and weak.

Examination revealed a grey haired woman, not obviously wasted or pigmented, with severe pallor of the skin and mucous membranes, and slight pitting œdema of legs and sacrum. Her heart was not enlarged, its sounds were normal. A few crepitations were audible at the lung bases. The central nervous system was clear. The systolic blood pressure was 140 and the diastolic 68 millimetres of mercury. The urine contained a trace of albumin.

On investigation of the chest with X rays, small basal effusions were found. The hæmoglobin content was 4·2 grammes *per centum*. The red cell count was 1,310,000 cells per cubic millimetre. The colour index was 1·15. The white cell count was 1,300 cells per cubic millimetre. Anisocytosis was present with macrocytosis and polychromasia; many hypersegmented polymorphonuclear forms were seen. The mean corpuscular volume was 115·7 cubic micromillimetres, the mean corpuscular hæmoglobin 35·7 micromicrogrammes, and the mean corpuscular hæmoglobin concentration 30·9%. The hæmatocrit reading was 22%. A fractional test meal examination revealed 60 units of free hydrochloric acid. Sigmoidoscopy revealed a normal bowel; hæmorrhoids were present. The biochemical findings (Table I) included hypoproteinæmia. Barium meal and barium enema findings were normal.

The patient had worked as a cook for several years and it was found that her diet had been grossly inadequate. She was considered to be suffering from

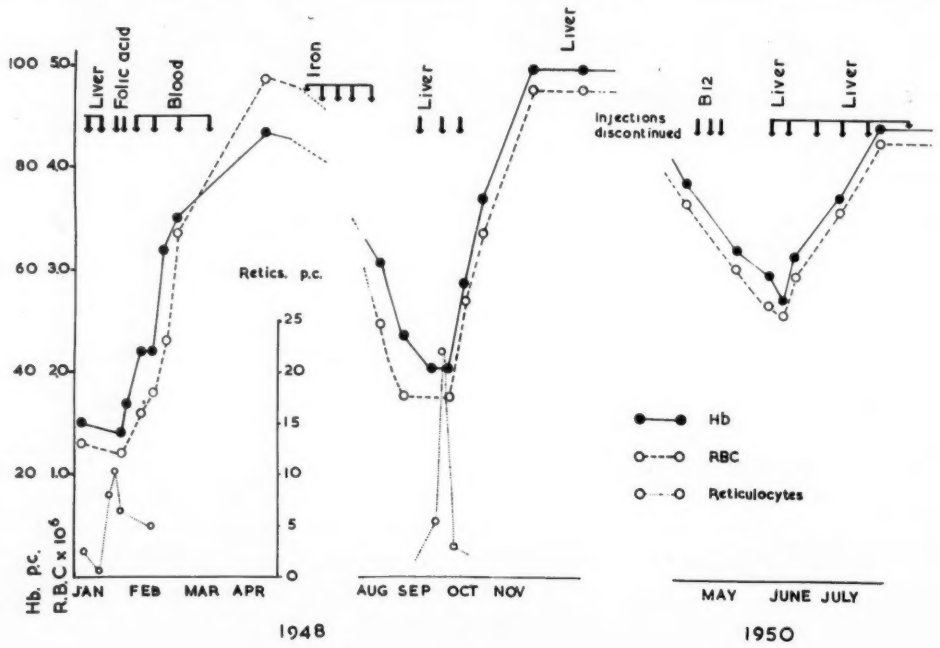

FIGURE I.

Case II, showing response to treatment over a period of observation of two years. Improvement on liver therapy on the patient's first admission to hospital was suboptimal, but in September 1948 she showed a prompt remission.

nutritional macrocytic anæmia and was given large intramuscular doses of crude liver extract. Although there was an appreciable reticulocyte response, there was no sustained improvement in the blood picture. Folic acid (20 milligrammes daily by mouth) also failed to induce a remission (Figure I). She developed severe pneumonia. There was a good response to antibiotics and repeated transfusions of packed red cells and whole blood. She was discharged from hospital on March 13, 1948, and was followed up in the out-patient clinic. Despite treatment with iron (given orally), vitamin *B* supplements, and a good diet, she rapidly went into hæmatological relapse, complaining of fatigue and sore tongue, and was readmitted to hospital on September 14, 1948.

On her second admission examination of her blood revealed a hæmoglobin content of 6·8 grammes *per centum*. The red cell count was 1,780,000 cells per

cubic millimetre. The colour index was 1·37. The white cell count was 4300 cells per cubic millimetre. Macrocytosis, anisocytosis and poikilocytosis were present. The hæmatocrit reading was 19%. The mean corpuscular volume was 112·4 cubic micromillimetres, the mean corpuscular hæmoglobin 37·8 micromicrogrammes, and the mean corpuscular hæmoglobin concentration 33·6%. On sternal marrow biopsy the erythroid : myeloid cell ratio was 3·3 : 4·0; the marrow was hyperplastic, with many megaloblasts present. Gastric biopsy revealed a normal gastric mucosa. The fasting gastric contents contained 36 units of free hydrochloric acid. The total serum protein content was 3·8 grammes *per centum*.

On this occasion there was an optimal response to liver therapy (" Campolon ") (Figure I) and the patient was discharged from hospital on November 14, 1948.

Throughout 1949 she continued to receive fortnightly injections of " Campolon " (10 cubic centimetres) and she remained in hæmatological remission. The diagnosis was reconsidered and tests clearly demonstrated defective intestinal absorption (Figures VI, VIII, IX). In March 1950 liver therapy was withheld and she went into relapse. In May, when the hæmoglobin value had fallen to 60%, weekly injections of vitamin *B12* were given, but failed to cause a remission. She also developed mild diarrhœa with symptoms of tetany and the serum calcium content fell to 4·8 milligrammes *per centum*. X-ray examination of bones showed mild generalized osteoporosis. When liver therapy was recommenced she showed a prompt remission, which has continued to date. In March 1951 symptoms of tetany returned and she was given large oral doses of calcium gluconate (60 grains daily) and calciferol, 200,000 international units by intramuscular injection twice weekly; symptoms became less and the level of serum calcium rose.

This was an interesting case of the idiopathic variety of the malabsorption syndrome in a patient who presented on two occasions with severe megaloblastic anæmia. A curious feature was the poor response to liver therapy on the occasion of her first admission to hospital, compared to subsequent liver-induced remissions. It is possible that this was a purely quantitative phenomenon for the combined effect of chronic blood loss, severe malnutrition and infection would be to increase greatly the requirements of hæmatinic principle.

Most of the characteristic clinical features of idiopathic steatorrhœa are illustrated in Case I. Diarrhœa had been present for at least thirty years and latterly the stools were of the typical pultaceous quality, but earlier it would seem that they were deceptively watery. Cooke, Frazer and their colleagues (Cooke *et alii*, 1946) have pointed out the many pitfalls in examining stools in patients with the malabsorption syndrome. Diarrhœa may be absent for long intervals, as in Case I, or if present, the stools may be watery rather than fatty. Even the appearance of a stool may be deceptive, for apparently normal fæces may contain an abnormally high quantity of fat.

Wasting in Case I was quite severe and pigmentation reminiscent of Addison's disease was present. This pigmentation, together with the glossitis, is probably due to a mixed vitamin *B* deficiency (Kaufman and Smith, 1943); thiamine excretion in this patient was remarkably low.

Disturbances of calcium metabolism, severe at a late date in Case II, were present in both patients. The association of tetany with diarrhœa was first recorded by Trousseau (1868). Severe osteomalacia with osteoporosis, causing bone pains and spontaneous fractures, may be a rare mode of presentation of the malabsorption syndrome (Snell, 1939). The negative calcium balance is due in part to impaired absorption of fat-soluble vitamin *D* and in part to precipitation of calcium as calcium soap.

The prothrombin index in Case I was significantly low (51%). Impaired absorption of fat-soluble vitamin *K* may cause a severe bleeding tendency: such cases have been described by Kark *et alii* (1940) and Fanconi (1938).

The anæmia in both these patients was macrocytic in character, and in Case II, unusually severe. Snell (1939) found a mean hæmoglobin content of 10·2 grammes *per centum* and a mean red cell count of 3,300,000 cells per cubic millimetre in twenty-two cases of idiopathic steatorrhœa; the anæmia was macrocytic in seventeen and hypochromic in five. These findings were substantially confirmed by Cooke *et alii* (1948) in an analysis of forty-five cases.

Case II exemplifies the difficulty experienced in diagnosing the true nature of a megaloblastic anæmia where defective absorption is not clinically obvious. Similar cases have been described by Davidson (1948) and by Israels and Sharp (1950). Sugar and fat tolerance curves are of great value in the elucidation of this difficult type of case. Wood and his colleagues (1950) have demonstrated the value of gastric biopsy in the diagnosis of pernicious anæmia and the syndrome of subacute combined degeneration of the cord, and it is clear that this technique has an important part to play in the differentiation of the megaloblastic anæmias. It is worthy of special note that the histological appearance of the gastric mucosa was quite normal in both these patients with the idiopathic variety of the malabsorption syndrome.

CASE III.—A male patient, aged forty years, was first admitted to hospital on June 10, 1950. In 1938 he had had a posterior gastro-enterostomy performed for chronic duodenal ulcer. Travelling by sea from

the United Kingdom to Australia, he had called at Malta, after which he developed a form of diarrhœa resembling dysentery. He was admitted to hospital on arrival in Melbourne. No pathogens were isolated from the fæces, and a barium meal revealed a functioning gastro-enterostomy with a normal stoma and a grossly distorted duodenal cap.

Admitted to hospital for a second time on October 6, 1950, he had complained of persistent diarrhœa and had lost three stone in weight despite an excellent appetite. His face, hands and feet were œdematous.

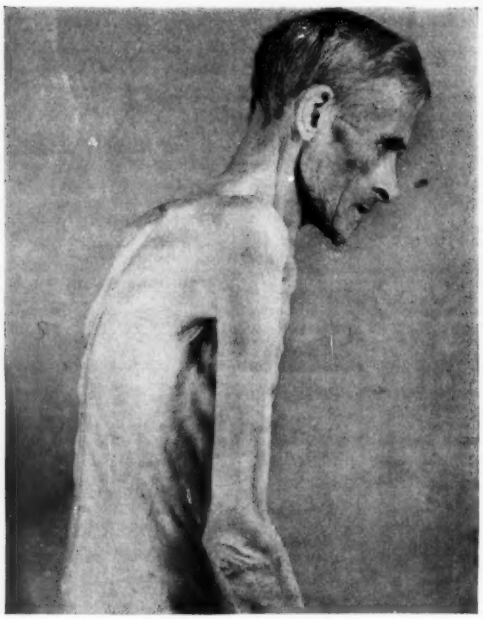

FIGURE II.

Case IV, showing extreme degree of emaciation in a patient with reticulosis of the mesenteric lymph nodes and the malabsorption syndrome.

Examination revealed severe wasting with pitting œdema of the legs. The systolic blood pressure was 130 and the diastolic 80 millimetres of mercury. The lungs, cardio-vascular system and central nervous system were normal.

On investigation the fæces were found to be pale and bulky; fat was 45% of the dry weight. Hæmoglobin content of the blood was 11·5 grammes *per centum*. The red cell count was 4,030,000 cells per cubic millimetre. The colour index was 0·97. The white cell count was 11,400 cells per cubic millimetre. Biochemical investigations (Table I) revealed hypoproteinæmia and hypoprothrombinæmia. The results of absorption tests are shown in Figures VI, VIII and IX. A barium meal showed no change from the appearances in June and a barium enema revealed a minor filling defect in the transverse colon. There was no evidence of reflux of barium into the stomach.

Despite clinical features which were suggestive of gastro-colic fistula the circumstances of the onset of the illness and the absence of radiological confirmation delayed a decision to operate. However, the patient became severely ill with intense diarrhœa and fæculent vomiting.

Operation was performed on December 12, 1950, by Mr. Paul Jones. A gastro-colic fistula at the site of the old anastomosis was found. The colon was repaired, the old posterior gastro-enterostomy was undone and subtotal gastrectomy with gastro-jejunostomy was performed.

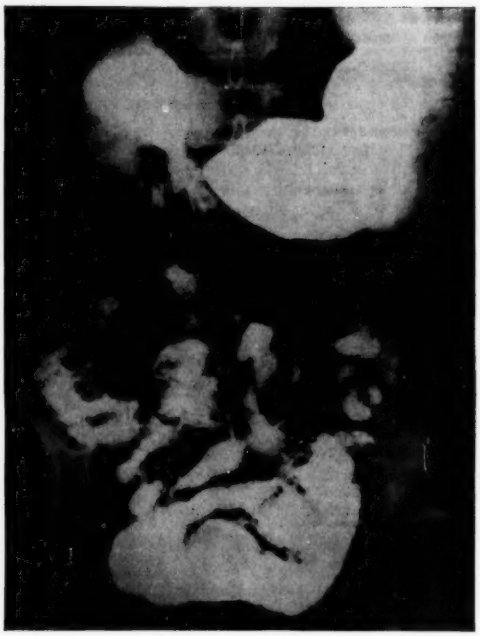

FIGURE III.

Case IV. Barium meal—appearances after six hours. The stomach is considerably dilated and only partly emptied. The first and second parts of the duodenum are dilated. The typical "deficiency pattern" of the ileum is also clearly shown.

Convalescence was hampered by thrombophlebitis and wound sepsis. In January 1951 the patient's nutritional status was still poor, with œdema and peripheral neuropathy, but great improvement took place in the ensuing months on a diet with a high caloric value and a high protein content with vitamin *B* supplements, and he regained his original strength and weight.

In summary, steatorrhœa, wasting and peripheral œdema occurred in a patient with a gastro-colic fistula not demonstrated radiologically.

CASE IV.—A male patient, aged fifty-eight years, was admitted to hospital on July 2, 1951. He had complained of diarrhœa for two years; at first this had been watery but later motions were semi-solid in consistency. His appetite was poor, and he had lost a considerable amount of weight. In November 1950 a diagnosis of idiopathic steatorrhœa had been made at another hospital, but he had not improved on a sprue diet. Before admission to hospital he developed cramps and paræsthesia, and had an epileptic seizure.

Examination showed the patient to be cachectic (Figure II) with pigmentation of face, arms and legs. Chvostek's sign was positive. The systolic blood pressure was 160 and the diastolic pressure 100 millimetres of mercury. Heart and lungs were normal.

On investigation the fæces were clay-coloured, the total fat being 36%. Examination of the blood revealed a hæmoglobin content of 11·1 grammes *per centum*. The red cell count was 4,200,000 cells per cubic millimetre. The colour index was 0·89. The white cell count was 6000 cells per cubic millimetre. Iliac crest biopsy revealed a moderately cellular normoblastic marrow. Histamine test meal showed no free hydrochloric acid but 50 units of total acid.

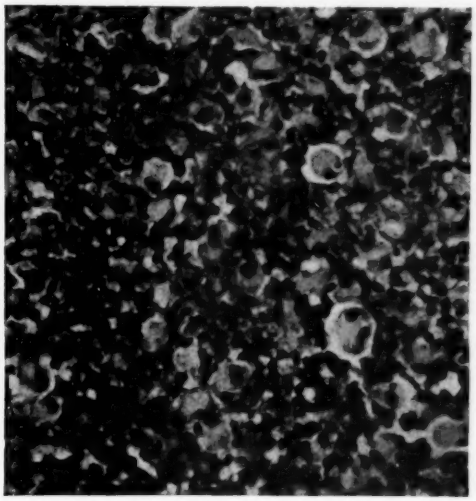

FIGURE IV.

Section of lymph node showing replacement of normal tissue by cells of reticulum and histiocytic type with a low grade of mitotic activity.

Biochemical investigations (Table I) revealed severe hypoproteinæmia and hypocalcæmia. Absorption tests (Figures VI and VII) revealed delayed absorption of glucose. Barium meal examination (Figure III) showed delayed gastric emptying and apparent partial obstruction of the second part of the duodenum.

Operation was performed on July 19, 1951, by Mr. Julian Smith. Numerous yellow rubbery enlarged lymph nodes, 0·5 to 2·0 centimetres in diameter, were seen throughout the mesentery. Liver and spleen were not involved. No obstruction of the duodenum was found, but a posterior gastro-enterostomy was performed in view of the radiological appearances.

Histological examination by Professor E. S. J. King (Figure IV) revealed appearances consistent with non-specific reticulosis, possibly Hodgkin's disease, with a relatively low grade of cellular activity.

After operation diarrhœa persisted and the appetite of the patient was severely depressed. He went into a decline and became moribund. As a last resort nitrogen mustard was given intravenously, 16 milligrammes in three divided doses. During this period generous infusions of blood, serum and protein hydrolysates were administered. Three further doses of mustard were subsequently given and intragastric drip feeding of high caloric milk mixture satisfactorily increased his weight. He was discharged from hospital on November 26, 1951. By April 1952 he had put on two and a half stone in weight and was considered fit for light employment. Since mustard therapy seems to have been successful in improving the patient's diarrhœa and general condition, it is proposed to readmit him to hospital at intervals for further therapy should this prove necessary.

In summary, steatorrhœa, tetany and cachexia developed in a man with reticulosis confined to the lymph nodes of the mesentery. Biochemical tests indicated intestinal malabsorption. Clinical improvement on nitrogen mustard therapy was dramatic.

Both these patients (Cases III and IV) illustrate how closely disease of the mesenteric lymph nodes or an intestinal short circuit may simulate the syndrome of idiopathic steatorrhœa. Since laparotomy was responsible for the final diagnosis in both cases and showed that active therapeutic measures could be taken, these cases carry an important message: laparotomy in itself is a relatively harmless procedure, and where there is any doubt about the diagnosis in an unexplained case of the malabsorption syndrome, it should be resorted to without delay.

Malabsorption following ulcer surgery is, of course, a well recognized complication. Fairley and Kilner (1931) described the sprue syndrome occurring with gastro-jejuno-colic fistula. A more unusual event is malabsorption occurring after inadvertent gastro-ileostomy at subtotal gastrectomy (Moretz, 1949; Cooley and Hartmann, 1951) or ileo-colostomy (Brown, 1949). A great deal of interest has centred on the macrocytic anæmia which may occur in these cases (Barker and Hummell, 1939).

Hodgkin's disease and the related reticuloses are rarely confined to the mesenteric lymph nodes, and Case IV is therefore of unusual interest. Fairley and Mackie (1937) described four similar cases: two of lymphoma, one of Hodgkin's disease and one of reticulosarcoma. A patient of Salvesen (1948) with malabsorption due to reticulosarcoma died from perforation of the bowel. Such cachectic patients do not easily withstand heavy X-irradiation of the abdomen and the success we have had with nitrogen mustard in Case IV, given in relatively small repeated doses, represents a therapeutic advance.

Results of Absorption Tests

Carbohydrate Absorption (Figure V). In Cases I and II, in the presence of idiopathic insufficiency, there were almost flat glucose tolerance curves, showing rises of only nine and 26 milligrammes *per centum* after the administration of 50 grammes of glucose.

In Case III, with a gastro-colic fistula, the patient had a very low fasting blood sugar, but showed a good rise of 100 milligrammes *per centum* returning to fasting level in one and a half hours.

The curve in Case IV, with reticulosis of the mesenteric lymph nodes, was unusual. The fasting level of glucose was 88 milligrammes *per centum*, rising slowly to a peak of 160 milligrammes *per centum* at the end of three hours. Improvement in the curve was noted after therapy (Figure VI), when the maximum rise was observed after one and a half hours.

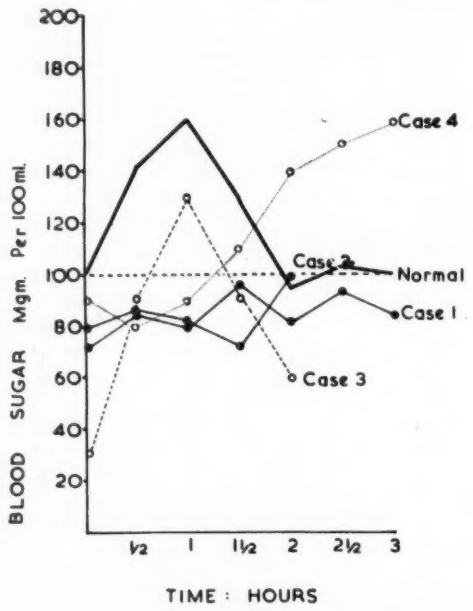

FIGURE V.
Sugar (oral) tolerance curves in four patients with the malabsorption syndrome.

Fat Absorption (Figure VII). One of the outstanding features in the biochemical picture of patients with the malabsorption syndrome, idiopathic or symptomatic, is the low level of total serum lipides (between 400 and 500 milligrammes *per centum*). The curve obtained after the oral administration of 50 grammes of butter fat is low and flat.

Protein Absorption (Figure VIII). The three patients on whom the oral glycine absorption test was performed showed a marked increase in the α-amino nitrogen. It appears that absorption of amino acid in these patients was in no way impaired.

DISCUSSION

Little difficulty is encountered in diagnosing the malabsorption syndrome when the more florid manifestations appear together; but it is likely that mild and atypical cases are commonly missed, and for this reason it is impossible to assess the incidence of the syndrome in the Australian community. The possibility of an underlying mechanism of intestinal malabsorption should be considered in a number of clinical contexts. Intermittent diarrhœa of unknown ætiology may be due to this cause (Case I) and it should be constantly borne in mind that "idiopathic steatorrhœa" is not a good descriptive term, because the stool may not always be obviously fatty in quality. A refractory iron deficiency or macrocytic anæmia (Case II) may be due to malabsorption and in these cases the performance of simple absorption tests may save months of conjecture. It is conceivable that an unexplained bleeding tendency due to hypoprothrombinæmia may occur from impaired absorption of vitamin *K*. Absorption tests play an important part also in the differential diagnosis of the syndrome of osteomalacia—bone pains, spontaneous fractures, radiological osteoporosis and Milkman pseudofractures,

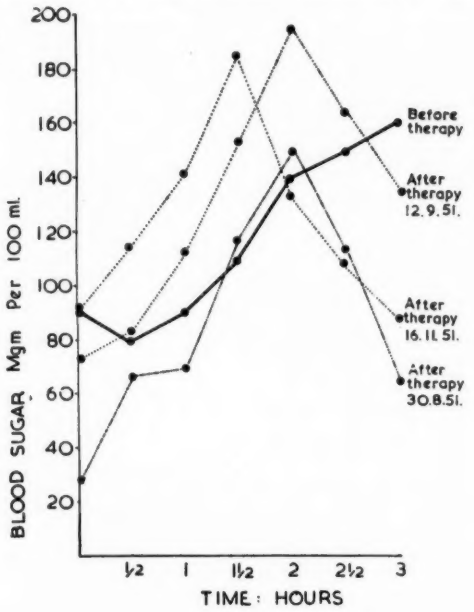

FIGURE VI.
Sugar (oral) tolerance curves in Case IV, before and after treatment with nitrogen mustard, showing a "shift to the left" towards a more normal curve.

hypocalcæmia and hypophosphatæmia. If these minor degrees of impaired absorption are borne in mind and these techniques of investigation are used, it is not unlikely that in the future many more cases will come to light.

The most important biochemical tests of malabsorption are estimation of the serum calcium and serum protein levels, which are both low, and the oral glucose and fat tolerance tests. An estimation of fat absorption is obligatory, since mere estimation of fat in the fæces is of limited value. Most other workers have preferred to employ the technique of five- or twelve-day quantitative fat balance tests (Cooke, Frazer *et alii*, 1946; Fourman, 1948) and have shown that less than 90% of fat is absorbed in the malabsorption syndrome. This

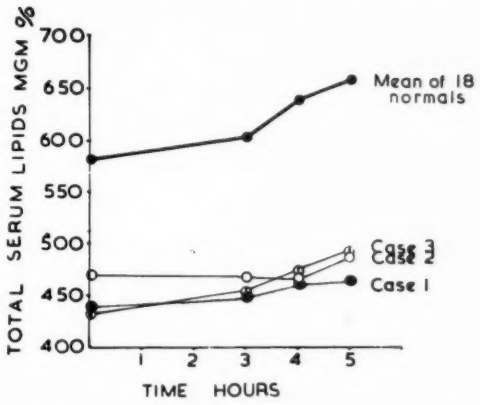

FIGURE VII.
Fat tolerance curves in three patients with the malabsorption syndrome.

technique is both time-consuming and tiresome and seems to have little practical advantage over the relatively simple oral butter test. The low fasting serum lipide level and the slight rise after the oral administration of 50 grammes of fat seem to be diagnostic of the malabsorption syndrome, particularly when the results of other investigations are also taken into consideration.

The differentiation of symptomatic from idiopathic cases is a matter of some importance. In our limited experience, symptomatic cases of the malabsorption syndrome appear to be as common in Australia—where sprue is not encountered—as cases of so-called " idiopathic steatorrhœa ". Perusal of the above case reports demonstrates how difficult differentiation may be on clinical grounds alone. Of possible significance is the fact that the shape of the sugar tolerance curves in Cases III and IV was not flat as in the idiopathic cases. The patient with the gastro-colic fistula showed a good rise from a low fasting level; and the curve of the patient with reticulosis seemed to demonstrate delayed rather than impaired absorption. Radiology is, of course, of considerable importance. In idiopathic steatorrhœa gastric dilatation and megacolon are often seen and indicate some degree of intestinal atony

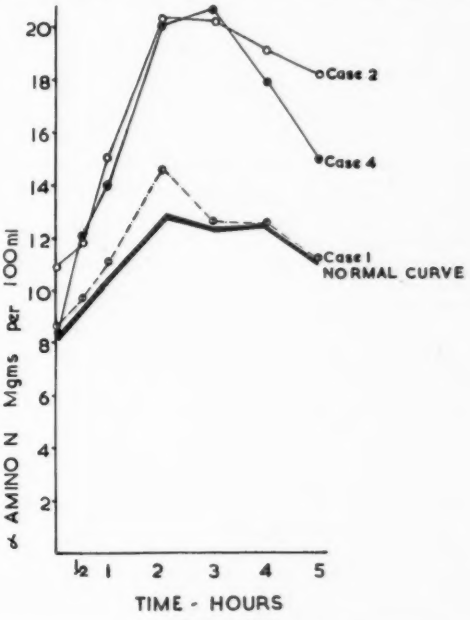

FIGURE VIII.
Glycine tolerance curves in three patients with the malabsorption syndrome.

(Snell and Camp, 1934; Kantor, 1940), and clumping of the barium in the small intestine (" deficiency pattern ", " moulage sign ") is also a diagnostic appearance. But these radiological signs may also be present in symptomatic cases, and one must in addition look for filling defects, internal fistulæ and other abnormal appearances which may point to the true diagnosis. Even so, a gastro-colic fistula may be intermittent and not readily demonstrable, as in Case III, and laparotomy is a justifiable court of appeal where doubt exists.

Classification which is not based on complete physiological understanding has a limited value; but it is possible to differentiate several mechanisms causing the same pattern of malabsorption. Reduction in length of the jejunum and ileum does not necessarily cause malabsorption, for Althausen and Weiden and their colleagues (1950) have demonstrated satisfactory restitution of intestinal absorptive

function after the massive resection of the small bowel in two cases, and cite other similar reports. On the other hand, deflection of the contents of the stomach into the colon, inadvertent gastro-terminal ileostomy, or ileocolostomy where the greater part of the small intestine is non-functioning, as in regional ileitis (Crohn's disease), commonly leads to steatorrhœa, wasting and macrocytic anæmia. Then there is the group of cases in which the absorption of fat is impaired by mechanical obstruction of the lacteals, as by tuberculosis, lymph-adenoma or reticulosarcoma affecting the mesenteric lymph nodes. In the idiopathic cases and in sprue it is necessary to resort to an hypothesis of an inherited or acquired biochemical lesion, in the absence of evidence of any demonstrable pathological lesion of the bowel (Fairley, 1937). The physiological anomaly is possibly that of defective phosphorylation of fatty acid and glucose in the intestinal mucosa (Stannus, 1942). Frazer (1949), on the other hand, had attempted to link all the observed facts in a theory of faulty particulate absorption of fat.

In the treatment of the malabsorption syndrome diet plays a rôle of fundamental importance. A low fat-high protein régime should be supplied, with generous vitamin supplements. When hypocalcæmia is severe it may be necessary to give vitamin *D* by intramuscular injection. Experience with specific hæmatinic substances has varied. For many years crude liver extracts were employed with variable success. Davidson, Girdwood and Innes (1947) found that folic acid failed to improve the blood picture in patients with the sprue syndrome; and that it was without effect on the amount of fat absorbed. Weir and Comfort's experience at the Mayo Clinic (1947) was essentially similar. Israels and Sharp (1950) and Tuck and Whittaker (1950) had unsatisfactory results treating megaloblastic anæmia of idiopathic steatorrhœa with pure vitamin *B*12. It is impossible, therefore, to lay down any hard and fast rules regarding therapy in the hæmatology of the malabsorption syndrome—the response to crude liver, folic acid or vitamin *B*12 can be estimated only by the method of trial and error.

SUMMARY

1. It is suggested that the term "malabsorption syndrome" should be used collectively to describe all cases of sprue, cœliac disease, idiopathic steatorrhœa and steatorrhœa complicating disease of the intestinal and mesenteric lymph nodes.

2. Four cases are described. Two were idiopathic in type, in one of which the patient presented in the first instance with megaloblastic anæmia and presented a difficult problem in diagnosis. Two cases were symptomatic. One of these patients had a gastro-colic fistula and was cured by operation; the other had reticulosis of the mesenteric lymph nodes and showed a remarkable clinical improvement with nitrogen mustard therapy.

3. The outstanding clinical features were loss of weight, often severe; intermittent diarrhœa; glossitis; latent tetany; and anæmia. Frank steatorrhœa was not invariably present in all stages of the disease.

4. The main biochemical features of the malabsorption syndrome are hypoproteinæmia, hypocalcæmia, hypoprothrombinæmia, an abnormal oral sugar tolerance curve, a low fasting level of total serum lipide and a flat oral fat tolerance curve.

5. These investigations are useful in the diagnosis of atypical syndromes of malabsorption. As a useful screening test of fat absorption the oral fat tolerance test is preferred to more complicated fat balance studies.

6. The possibility of intestinal malabsorption is to be considered in obscure cases of recurrent diarrhœa, refractory megaloblastic anæmia, and osteomalacia.

7. The value of exploratory laparotomy is stressed in regard to diagnosis.

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REFERENCES

ALTHAUSEN, T. L., DOIG, R. K., UYEYAMA, R., and WEIDEN, S. (1950), "Digestion and Absorption after Massive Reaction of the Small Intestine", *Gastroenterology*, **16**, 126.

AMSTERDAM, H. J., and GRAYZEL, D. M. (1945), "Intestinal Lipodystrophy", *Am. J. M. Sc.*, **210**, 605.

ANFANGER, H., and HEAVENRICH, R. M. (1949), "Amino Acid Tolerance Test in Children", *Am. J. Dis. Child.*, **77**, 425.

BARKER, W. H., and HUMMEL, L. E. (1939), "Macrocytic Anæmia Associated with Intestinal Strictures and Anastomoses", *Bull. Johns Hopkins Hosp.*, **64**, 133.

BENNET, T. I., HUNTER, D., and VAUGHAN, J. M. (1932), "Idiopathic Steatorrhœa", *Quart. J. Med.*, **1** (N.S.), 603.

BROWN, A. (1949), "Steatorrhœa and Glossitis after Ileocolostomy", *Brit. M. J.*, **1**, 1073.

COOKE, W. T., ELKES, J. J., FRAZER, A. C., PARKES, J., PEENEY, A. L. P., SAMMONS, H. G., and THOMAS, G. (1946), "Anomalies of Intestinal Absorption of Fat: Determination of Significance of Fæcal Fat", *Quart. J. Med.* **15** (N.S.), 141.

COOKE, W. T., FRAZER, A. C., PEENEY, A. L. P., SAMMONS, H. G., and THOMPSON, M. D. (1948), "Anomalies of Intestinal Absorption of Fat: The Hæmatology of Idiopathic Steatorrhœa", *Quart. J. Med.*, **17** (N.S.), 9.

COOLEY, D. A., and HARTMANN, R. C. (1951), "Inadvertent Gastro-ileostomy", *Bull. Johns Hopkins Hosp.*, **89**, 133.

DAVIDSON, L. S. P., GIRDWOOD, R. H., and INNES, E. M. (1947), "Folic Acid and the Treatment of the Sprue Syndrome", *Lancet*, **7**, 511.

DAVIDSON, L. S. P. (1948), "Refractory Megaloblastic Anæmia", *Blood*, **3**, 107.

DOIG, R. M., MOTTERAM, R., ROBERTSON, E. G., and WOOD, I. J. (1950), "The Early Diagnosis of Subacute Combined Degeneration of the Cord: Value of Gastric Biopsy", *Lancet*, **2**, 836.

FAIRLEY, N. H. (1930), "Sprue: Its Applied Pathology, Biochemistry and Treatment", *Tr. Roy. Soc. Trop. Med. and Hyg.*, **34**, 131.

FAIRLEY, N. H., and KILNER, J. P. (1931), "Gastro-Jejuno-Colic Fistula with Megalocytic Anæmia Simulating Sprue", *Lancet*, **2**, 1335.

FAIRLEY, N. H. (1937), "Tropical Sprue with Reference to Intestinal Absorption", *Tr. Roy. Soc. Trop. Med. and Hyg.*, **30**, 9.

FAIRLEY, N. H., and MACKIE, F. P. (1937), "The Clinical and Biochemical Syndrome of Lymphadenoma and Allied Diseases Involving the Mesenteric Lymph Nodes", *Brit. M. J.*, **1**, 374.

FANCONI, G. (1938), "*Zöliakie*", *Deutsche med. Wchnschr.*, **64**, 1565.

FOURMAN, L. P. R., HIGGINS, G., QUELCH, P., O'BRIEN, J. P. R., and WITTS, L. J. (1948), "Investigation and Diagnosis of Steatorrhœa", *Clin. Sc.*, **7**, 121.

FRAZER, A. C. (1949), "Fat Metabolism and the Sprue Syndrome", *Brit. M. J.*, **2**, 767.

GEE, D. (1888), "On Cœliac Affection", *St. Bart. Hosp. Rep.*, **24**, 17.

HERTER, C. A. (1908), "On Infantilism from Chronic Intestinal Infection", New York.

HURST, A., PAYLING WRIGHT, G., and RYLE, J. A. (1942), "Sprue Syndrome from Obstruction of the Lacteals by Chronic Tuberculosis of the Mesenteric Lymph Nodes", *Guy's Hosp. Rep.*, **91**, 25.

ISRAELS, M. C. G., and SHARP, J. (1950), "Idiopathic Steatorrhœa with Megaloblastic Anæmia", *Lancet*, **1**, 752.

KANTOR, J. L. (1940), "Further Experience with the Roentgen Diagnosis of Idiopathic Steatorrhœa", *Arch. Int. Med.*, **65**, 988.

KARK, R., SOUTER, A. W., and HAYWARD, J. C. (1940), "A Hæmorrhagic Diathesis with Idiopathic Steatorrhœa", *Quart. J. Med.*, **9** (N.S.), 247.

KARK, R., and LOZNER, E. L. (1939), "Nutritional Deficiency of Vitamin *K* in Man", *Lancet*, **2**, 1162.

KAUFMAN, W. H., and SMITH, D. C. (1943), "The Sprue Syndrome", *J.A.M.A.*, **131**, 168.

KUNKEL, H. G., AHRENS, E. H., and EISENMENGER, W. G. (1948), "Application of Turbidimetric Methods for the Estimation of Gamma Globulin and Total Lipid in the Study of Patients with Liver Disease", *Gastroenterology*, **11**, 499.

LEISHMAN, A. W. D. (1945), "Thoughts on Sprue", *Lancet*, **2**, 813.

MENDEZ-FERRIERA, H. E., and BARGEN, J. A. (1937), "So-called Non-Tropical Sprue Associated with Tuberculosis of the Lymph Nodes", *Proc. Staff Meet. Mayo Clin.*, **12**, 287.

MORETZ, W. H. (1949), "Inadvertent Gastro-ileostomy", *Ann. Surg.* **130**, 124.

NYMAN, E. (1949), "Ulcerous Jejuno-Ileitis with Symptomatic Sprue", *Acta med. Scandinav.*, **135**, 275.

SALVESEN, H. A. (1948), "Symptomatic Sprue Due to Reticulo-Sarcomatosis of the Small Intestine", *Gastroenterologia*, **73**, 166.

SNELL, A. M., and CAMP, J. D. (1934), "Chronic Idiopathic Steatorrhœa: Roentgenologic Observations", *Arch. Int. Med.*, **53**, 615.

SNELL, A. M. (1939), "Tropical and Non-Tropical Sprue", *Ann. Int. Med.*, **12**, 1632.

STANNUS, H. S. (1942-43), "Sprue", *Tr. Roy. Soc. Trop. Med. and Hyg.*, **36**, 123.

THAYSEN, H. E. H. (1935), "Ten Cases of Idiopathic Steatorrhœa", *Quart. J. Med.*, **4** (N.S.), 359.

TROUSSEAU, A. (1868), "Lectures on Clinical Medicine", The New Sydenham Society, London, **35**, 373.

TUCK, I. M., and WHITTAKER, N. (1950), "Vitamin B12 in Idiopathic Steatorrhœa", *Lancet*, **1**, 757.

WEIR, J. F., and COMFORT, M. W. (1947), "Folic Acid Therapy in Non-Tropical Sprue: Results of Treatment in Seven Cases", *J. Lab. and Clin. Med.*, **32**, 1231.

WHIPPLE, G. H. (1907), "A Hitherto Undescribed Disease Characterised Anatomically by Deposits of Fat and Fatty Acid in the Intestinal and Mesenteric Lymphatic Tissues", *Bull. Johns Hopkins Hosp.*, **18**, 382.

WOOD, I. J., DOIG, R. K., MOTTERAM, R., and HUGHES, A. (1949), "Report on 55 Biopsies using a New Flexible Gastric Biopsy Tube", *Lancet*, **1**, 18.

WOODRUFF, A. W. (1949), "Ætiological and Prognostic Features in Tropical Sprue", *Tr. Roy. Soc. Trop. Med. and Hyg.*, **42**, 605.

DISSECTING ANEURYSM OF THE AORTA CONFIRMED BY ANGIOCARDIOGRAPHY

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Over the past two decades the diagnosis of dissecting aneurysm during life has become increasingly common. In the 300 cases reviewed by Shennan (1934) only seven were diagnosed *ante mortem*, yet Weisman and Adams (1944) reported 55% correct diagnoses over the preceding ten-year period. This improvement has been due to increasing awareness of the condition and its variable but characteristic symptoms. In the following case the diagnosis of dissecting aneurysm was not suspected until proved by angiocardiography.

Case History

M.Q., a housewife, first came under medical attention in 1946 at the age of fifty-five years. She was admitted to hospital with erysipelas and during the routine examination a systolic blood pressure exceeding 200 millimetres of mercury was noted. After her discharge from hospital she had intermittent treatment of the condition over several years. Her systolic blood pressure remained in excess of 200 millimetres of mercury, but exact details are not known. She was free of symptoms over the period and led a normal, active life.

On the evening of December 11, 1950, while sitting quietly in a chair, she was suddenly seized with a severe crushing pain behind the centre of the sternum passing through to the back. The onset was so rapid that she felt as though she had been shot through the chest. There was no radiation other than to the back. She felt weak and shaky and sweated excessively. Her medical practitioner was called and the injection of one-quarter grain of morphine followed shortly afterwards by 100 milligrammes of pethidine gave some relief, although still uncomfortable, she was able to rest. The following morning she was admitted to another hospital with a provisional diagnosis of coronary occlusion. The pain had eased by the time of her admission to hospital. The systolic blood pressure was recorded as 140, and the diastolic pressure as 100 millimetres of mercury. An electrocardiogram showed left axis deviation and some myocardial damage, but no evidence of any recent ischæmic episode.

After three days in hospital she became increasingly short of breath and developed an intermittent pyrexia up to 102·5° F. The clinical signs of fluid were detected on the left side of the chest. She was treated with sulphadiazine, penicillin and streptomycin without any improvement. An X-ray examination of the chest on December 28, 1950, revealed a large pleural effusion on the left side with considerable displacement of the mediastinum towards the right. *Paracentesis thoracis* was performed on December 30, 1950, and repeated on January 2, 1951. On each occasion approximately 15 ounces of heavily blood-stained fluid were removed. On pathological examination the fluid showed a few lymphocytes, but there was no growth of organisms on culture. A further X-ray examination of the chest was taken on January 4 (Figure I). A large effusion was still present with an overlying pneumothorax. In addition the superior mediastinum was widened, suggesting a possible mediastinal tumour. In a subsequent X-ray examination eight days later this enlargement was more pronounced and it was considered that the diagnosis of

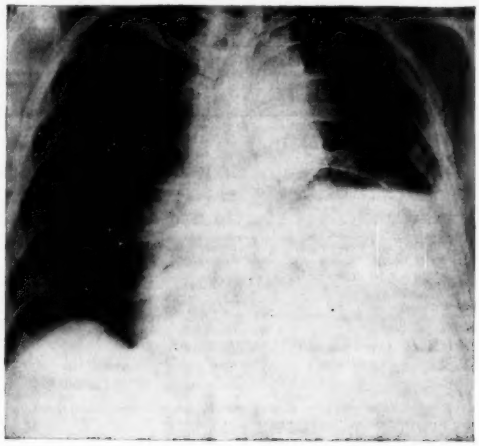

Figure I.

carcinoma of the lung was most likely. In early February a bronchogram was performed (Figure II). The trachea was seen to be displaced to the right and compressed. The left upper lobe bronchus was not filled, and the left lower lobe bronchus but poorly. This was felt to confirm the diagnosis of carcinoma of the left upper lobe bronchus. Bronchoscopy was attempted one week later, but the left main stem bronchus could not be entered. It was about this time that hoarseness of the voice was noted and this persisted over the ensuing months. Nothing further was done and the patient was discharged to a convalescent home on March 4, 1951.

On April 11 she was admitted to the Thoracic Unit, Royal Prince Alfred Hospital, for further investigation of the chest condition. At this time, apart from the hoarseness, she was free of symptoms. On examination the systolic blood pressure was 235, and the diastolic pressure 130 millimetres of mercury in both arms.

The apex beat was in the sixth left intercostal space, four and a half inches from the mid-line. No murmurs were present. There was still some diminution of movement, dulness to percussion, and reduction of breath sounds at the left base. Examination of the larynx showed a complete paralysis of the left vocal cord. Further X-ray pictures were taken (Figure III), and fluoroscopy was carried out. The radiologist reported :

> There is a large rounded tumour of the upper left hemithorax which occupies almost the entire subapical region of the left lung field. It involves the upper mediastinum and the hilar region and is somewhat posteriorly placed. It does not pulsate, but it displaces the œsophagus to the right and the œsophagus curves regularly around it. Even in the absence of pulsation the appearances are still those of aneurysm.

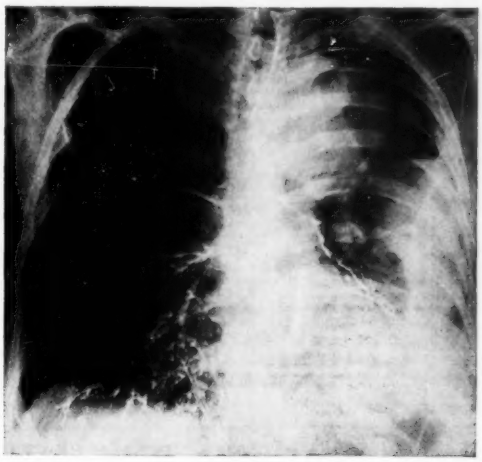

FIGURE II.

On April 18 a bronchoscopy was performed. The mucosa of the left main bronchus was very œdematous and swollen, but apart from prominent arterial pulsations no other abnormalities were noted. The response to the Wassermann test was negative. After the above investigations it was felt that the lesion was probably aneurysmal in nature but certain features seemed anomalous. The patient was then referred to the Hallstrom Institute of Cardiology for investigation. Angiocardiography was carried out on May 5, 1951, almost six months after the initial onset of her symptoms.

The arm-tongue time was estimated using 50 cubic centimetres of a solution of saccharine and this was injected in two seconds. By doing this, the altered hæmodynamics present during the actual injection of the dye was reproduced, and the time estimated—10·6 seconds—gave a reasonable guide to the ideal exposure times to obtain views of the left side of the heart and the aorta. Fifty cubic centimetres of a 70% solution of diodrast were then injected into the right basilic vein in two seconds with the patient in the prone position on the X-ray table. Films were taken with overhead tube at intervals of 2, 4, 8, 10, 12 and 14 seconds from the commencement of the injection.

The first two films showed a normal right side of the heart. The third film (Figure IVA), taken eight seconds from the commencement of injection, showed dye in the pulmonary veins, the left-sided chambers of the heart and in the aorta. The ascending aorta appeared slightly dilated and from there the dye was seen to pass downwards in a very much narrowed channel on the medial side of the mediastinal mass. The appearance was seen better in the subsequent two films (Figures IVB and IVC). This medial channel was more clearly defined, and the dye then appeared in progressively increasing concentration in the more lateral portion of the mass. A clear line of demarcation was seen between the two areas. The mass did not fill to its lateral extent.

The interpretation placed on these findings was that the medial channel represented the true aortic lumen,

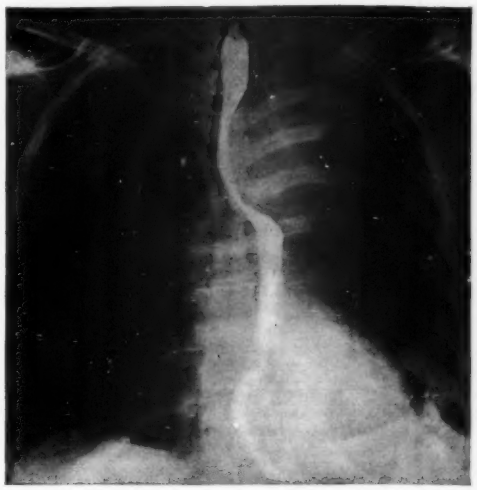

FIGURE III.

and the lateral portion of the aneurysmal sac within the aortic wall. The line of demarcation was due to the intima and portion of media dividing the two. The aneurysm extended from the arch to the lower edge of the film close to the diaphragmatic level. The findings were thus indicative of a dissecting aneurysm.

The patient was discharged from hospital shortly afterwards. She was well until September 1951, when she had a small hæmoptysis. This cleared quickly, and nothing further occurred until November 11, 1951, when she had a sudden massive hæmoptysis, and died within a few minutes. Post-mortem examination was refused.

DISCUSSION

In retrospect the clinical features in the early period of the patient's illness were consistent with the diagnosis of dissecting aneurysm. She was known to have been hypertensive for some years, and was in the sixth decade—the time of maximal incidence of this condition. The situation and character

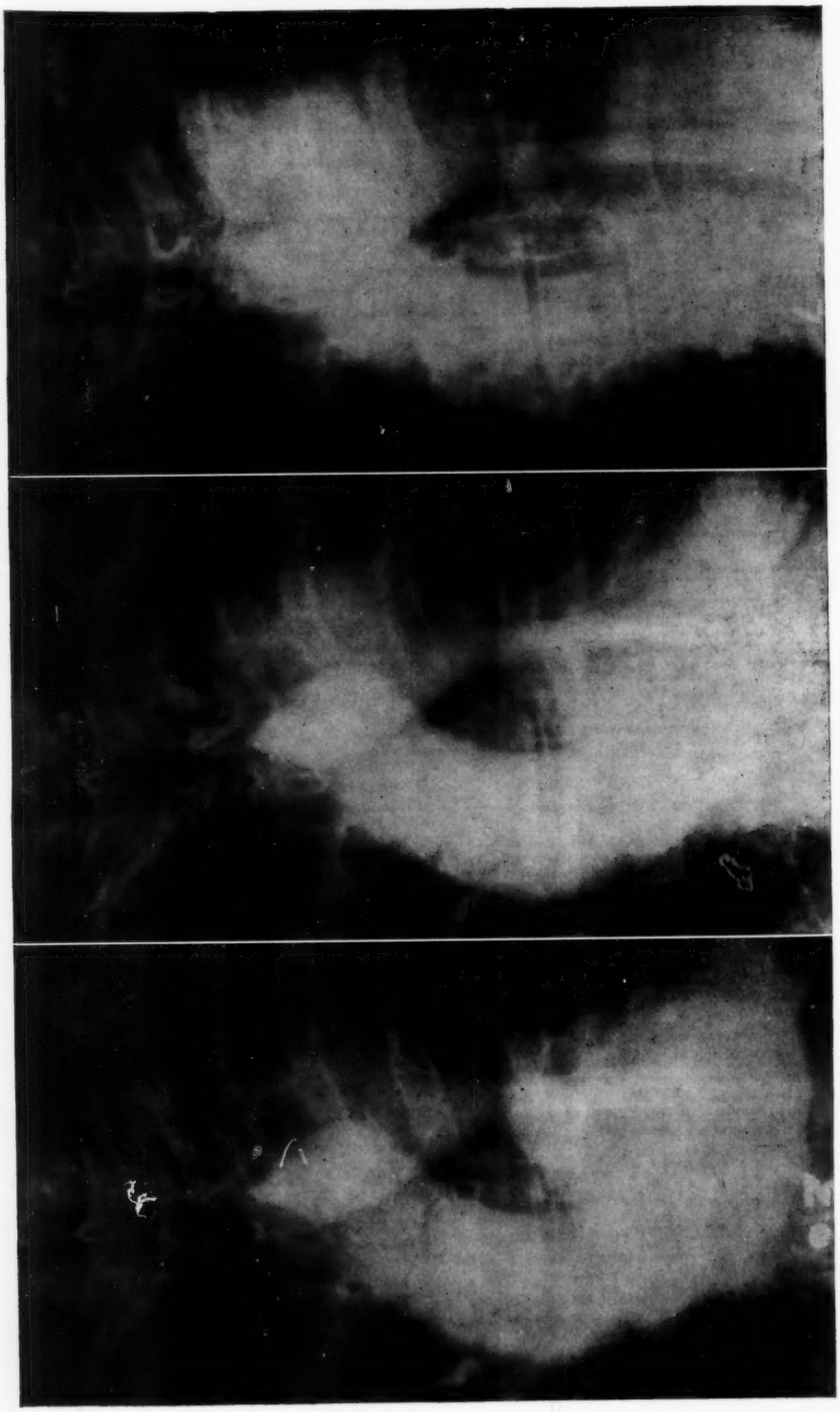

FIGURE IVC.

FIGURE IVB.

FIGURE IVA.

of the pain were classical. Her own description of feeling as if she were shot through the chest from front to back illustrated well the site and rapidity of onset of the pain. The subsequent development of a heavily-bloodstained pleural effusion with evidence of mediastinal enlargement in the region of the aortic arch followed a known course of the disease.

As, however, the possibility of this diagnosis was not considered in the early stages, the details of this part of the clinical history were rather pushed into the background, and the problem was considered merely as a mediastinal tumour with a complicating pleural effusion. It was thus that the patient was referred after some months, with a provisional diagnosis of carcinoma of the lung.

The presentation of dissecting aneurysm as a " mediastinal tumour " is not rare, particularly in those cases in which the onset lacks its usual severity. One such case has been seen previously at the Royal Prince Alfred Hospital, and it was included in a series of cases reviewed by Halliday and Robertson in 1946. The presenting symptoms were substernal pain over a period of two months and progressive dysphagia and dyspnœa for one month. An X-ray examination revealed a large mass in the posterior and middle mediastinum around the large vessels, and constricting the œsophagus. The condition was considered to be a mediastinal neoplasm, but the patient died suddenly, and post-mortem examination revealed a dissecting aneurysm which had ruptured terminally in the right pleural cavity.

In the case reported by Patrick and Taylor (1929) the patient developed progressive dysphagia and X-ray examination revealed a large non-pulsating mass displacing the œsophagus forwards and to the left. Thoracotomy was performed, and the mass incised with a resultant massive hæmorrhage and subsequent death.

Further evidence of the possible risks with this type of case was seen in the case reported by Chandler-Smith and Sancetta (1950). The patient was suffering from pulmonary tuberculosis and had bilateral artificial pneumothorax. The patient developed intermittent substernal pain unrelated to exertion, followed by a more severe attack with radiation to the neck and left arm, and associated with dyspnœa. The pain subsided in four days, but the dyspnœa persisted. X-ray examination of the chest revealed a convex bulge of the right border of the mediastinum at the level of the hilum of the right lung. This was regarded as a paramediastinal effusion, and an attempt was made to aspirate it. Blood was obtained, and the patient died ten minutes later from cardiac tamponade. At post-mortem examination the dissecting aneurysm was found to be confined to the media, and no intimal tear was present.

It is in cases belonging to this group that angiocardiography appears to have its place as a diagnostic aid. It may enable an exact diagnosis to be confirmed, and save unnecessary operations and possible disasters such as those recorded above. However, there are certain limitations which must be appreciated. A successful result depends on obtaining an adequate concentration of dye in the aneurysmal sac. Under three conditions this will be impossible: (*a*) If the sac is filled with blood clot. (*b*) If the intimal tear is too small to allow a reasonable concentration of the dye to accumulate in the sac. (*c*) If, as is seen in a small percentage of cases, no intimal tear is present.

The case of Chandler-Smith and Sancetta belonged to the latter group, and angiocardiography might have given a false negative result.

As to the risk of the procedure in these cases, evidence shows that the pressure falls following the injection, thus not increasing the possibility of further splitting. Realizing the tendency to spontaneous rupture of these aneurysms, it would appear advisable to delay the procedure if the condition was of recent onset, or if any progressive changes in its size were noted.

Notwithstanding the limitations and difficulties mentioned, angiocardiography appears to have a definite place in the investigation and diagnosis of these cases. This case is presented as no previous records of this use of angiocardiography could be discovered, and the case appeared to illustrate well the successful use of the procedure.

SUMMARY

1. A case of dissecting aneurysm is presented in which the diagnosis was confirmed by angiocardiography.

2. Some of the indications for the use of the procedure are discussed, together with its difficulties and limitations.

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REFERENCES

CHANDLER-SMITH, J., and SANCETTA, S. M. (1950), "Healed Dissecting Aneurysm of the Aorta Erroneously Diagnosed Para-mediastinal Effusion, Death following Attempted Aspiration", *Circulation*, **1**, 792.

HALLIDAY, J. H., and ROBERTSON, J. S. (1946), "Dissecting Aneurysm of the Aorta", *Proc. Roy. Australasian. Coll. Physicians*, **1**, 1.

PATRICK, C. V., and TAYLOR, J. F. (1929), "A Case of Dissecting Aneurysm of the Aorta", *Lancet*, **1**, 181.

SHENNAN, T. (1934), "Dissecting Aneurysms", Med. Research Council Special Report Series, 193.

WEISMAN, A. D., and ADAMS, R. D. (1944), "Neurological Complications of Dissecting Aneurysm", *Brain*, **67**, 69.

THE PELGER–HUET ANOMALY OF THE LEUCOCYTES

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PELGER'S congenital anomaly of the leucocytes, although not a widely recognized condition, is of great importance both in clinical medicine and in genetics.

The condition is unmistakable when once the Pelger-Huet cells have been recognized in the blood films. Briefly the change consists of an inhibition of the segmentation of the neutrophile nucleus so that, in the blood picture, the single lobed and two lobed neutrophile cells predominate. Only an occasional form is seen with a three lobed nucleus. This immaturity of the nuclear form is, however, contradicted by the maturity of the nuclear structure.

The nucleus shows a wealth of chromatin present in large moulded clumps. Some of the cells have the nucleus shaped like a peanut or dumb-bell; others have a typical pinc-nez appearance, which is also frequently seen in the eosinophile cells of normal blood. In other words, there is a dissociation between the maturity of the form and structure.

The family herewith reported was discovered during the routine examination of one member. Five generations were traced and as far as can be ascertained, the lineage is of British stock.

The abnormal cells were found in three generations — the grandmother, her two daughters, and two granddaughters. Two other granddaughters and a grandson had normal blood pictures, and one granddaughter was dead.

The medical history of the family is as follows:

First Generation Examined. A grandmother, seventy-eight years of age, states that she is quite well and has rarely consulted a doctor. The anomaly was present in her blood.

Second Generation. Mrs. R., the elder daughter, was in normal health and had no history of serious illness. Her blood showed the anomaly.

Mrs. Y., the other daughter and mother of the grandchildren, was seen in August 1949 with a history of excessive fatigue and sore throats. Her blood pressure was normal. Sugar was present in her urine, and a glucose tolerance test showed a mild disturbance of carbohydrate metabolism. Previous to this her health had always been good. Her blood was affected.

Third Generation. 1. The eldest grandchild, a female, was dead. The medical history showed that she had suffered from severe menstrual disturbances, with scanty and infrequent periods. In 1937, at the age of nineteen, she complained of pain in the lower part of the abdomen and back. Examined by Dr. B. T. Edye, she was found to have adenocarcinoma of the rectum. A resection was performed, but she died in 1944, apparently of metastases. By the courtesy of Dr. Edye, a copy of the leucocyte count was obtained. The total white cell count was 7,700 per cubic millimetre and of the 60% neutrophile cells 40 were band forms and 22 segmented, so that in all probability this patient also showed the anomaly.

2. Mrs. C., a female, the second child, was seen in August 1949, aged twenty-five years, complaining of sterility. No menstrual periods occurred until she was seventeen years of age, when after hormonal treatment she had three scanty periods. Her breasts were small and body hair was meagre. The glucose tolerance test gave a normal result. Her basal metabolic rate was −21%. A blood count disclosed the Pelger-Huet anomaly of the leucocytes, and this led to the examination of the relatives.

3. A third grandchild, a female, aged twenty-three years, was resident in another State. However, blood films were obtained, which showed no abnormality.

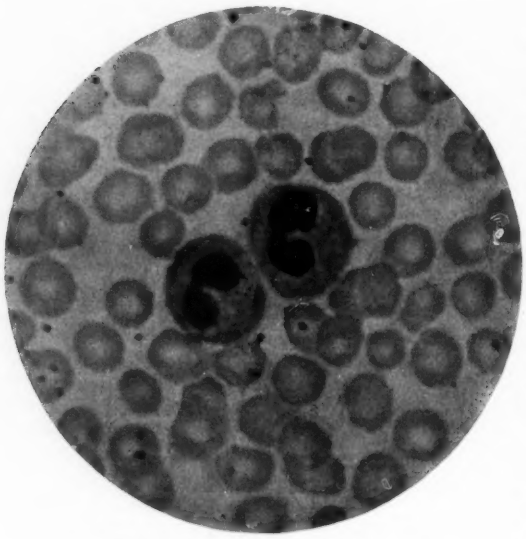
4. A fourth grandchild, a female, aged twenty years, M.Y., was unmarried. She had been treated during the last three years for *diabetes mellitus*. The appearance of this girl suggested some pituitary dysfunction. Her blood showed the anomaly.

5. A fifth grandchild, W.Y., a male, aged eighteen years, was in good health, and had a normal blood picture.

6. A sixth grandchild, a female, L.Y., aged fourteen years, had a normal blood picture,

and nothing abnormal could be detected on clinical examination.

The blood films from the father of these six members of the third generation were normal.



Photomicrograph of the Pelger-Huet cells from Mrs. C.

Differential leucocyte counts for each of the five affected members are shown in Table I, Figure I is a photomicrograph of the Pelger-Huet cells from Mrs. C.

It was impossible to examine the bone marrow of any of these persons, but full descriptions have been given by Undritz (1937), Stodtmeister (1936), Tischendorf (1939), Rohr (1949) and Leitner (1949).

Marrow preparations from the homozygous Pelger rabbits, to be discussed later, were also examined by Undritz (1943).

Review of the Literature

The Pelger-Huet anomaly of the leucocytes was first demonstrated by Pelger, a Dutch hæmatologist, in 1928. In 1931 he reported a second case, and Huet (1931) found similar cells in a niece of one of Pelger's patients which led to the examination of the remaining relatives and the finding of other affected members, whom Huet reported with two more families from Holland in 1932. In the same year the publications of Burger and Jordans appeared, and in 1933 Undritz described a family from Switzerland with what he then called the pseudo-regenerative white blood cell picture, and Schilling (1933) fully investigated two new families, one from Czechoslovakia and one from Germany (Weigeldt, 1933). It was Schilling who first suggested that the unusual change in the white cells be termed the Pelger-Huet anomaly of the leucocytes.

Two other families were found at this time, one by Huet and one by Hadorn, the details of which were not published until 1937 by Undritz (1937).

Naegeli (1934), Leitner and Van Leeuwen (1935), Dietzel (1925), Zundel (1935) and Peterson (1935) reported families with the same blood picture, that of Leitner and Van Leeuwen (1935) being the first family reported completely free of history or symptoms of tuberculosis, and Peterson's (1935) family was Chinese, resident in America.

In 1936 the literature was enriched by further reports. Schilling (1936) commented on an example of the characteristic cells found in a

Table I

Blood Counts of the Affected Members

Name.	Neutrophile Cells.				Lympho-cytes.	Mono-cytes.	Eosinophile Cells.	Total.
	Round.	One Lobe.	Two Lobes.	Three Lobes.				
First generation—								
Great grandmother	1	27	29	3	29	8	3[1]	8,200
Second generation—								
Daughter, Mrs. R., sister to Mrs. Y.[2]	2	44	36	—	15	2	1	8,000
Daughter, Mrs. Y.	1	44	33	—	16	5	1	8,000
Third generation—								
Mrs. C., granddaughter	2	33	21	1	26	6	11[3]	6,800
M.Y., granddaughter	1	21	32	2	38	3	3	7,600

[1] One with round nucleus.

[2] One perfect twin cell was seen in this film.

[3] Five with round nucleus.

native of Java by den Hartog Jager (1936). Alieff and Reekers (1936) discovered a family with thirteen affected members in three generations, and Roos (1936) reported another from Holland. Stahel (1936) discussed what at the time was believed to be a sporadic example of the anomaly without the condition being demonstrable in either of the parents, but later Undritz (1943) reexamined these blood films and found that both parents were " partial carriers ". The same was found to be true for the sporadic case reported by Zundel (1936).

A single case was found in France by Chevallier and Ely (1936) and Kokubo (1936) reported an interesting Japanese family with the anomaly. Eight were typical examples, and four what he termed " half typical ".

Undritz (1937) saw a patient who had " Pelger " cells present, but also normal cells, and described the person with this variation of the anomaly as a " *Teilträger* ", translated by Leitner (1949) as " a partial carrier ".

Lorenz (1937), who found the Pelger cells in five members of a family of eight, regarded them as a degenerative phenomenon and also believed the cells to be of great importance in genetics.

Tileston's report (1937) covered the first example in a patient of English ancestry, but unfortunately no direct descendants could be seen. Another German family was discovered by Ludtmann (1937).

It was in 1938 that Leitner stressed the dissociation between the form of the nucleus and its structural maturity in these cells, also describing three further families, and Hadorn and Blum's publication appeared the same year (1938).

Two families were reported by Tischendorf (1939) with the anomaly involving the neutrophile cells, eosinophile cells, basophile cells, and monocytes, and Huber's case (1939) is unique in that the patient was suffering from chronic myelosis, and also showed the Pelger cells. One daughter showed the anomaly, but the other six children were normal.

Kokubo (1939) found a second Japanese family, and added some data about his first report.

In 1939, Pelger cells were first found in the blood of animals by Knoll and Schmidt and Schmidt (1939), and Undritz (1939) having found them in rabbits, commenced his work on the importance of these cells in comparative hæmatology.

Only four other reports of the Pelger-Huet anomaly in human blood are present in the literature, namely those of Van der Sar (1944), Jonsson, Bostrom and Bringel (1948), Wegmann (1948) and Gramiccia (1951).

DISCUSSION

Huet (1932) was the first to point out the hereditary nature of this deviation from normal of the neutrophile cells. His first reported patient, a girl of seven, proved on further inquiry to be a niece of the patient reported by Pelger, and the phenomenon was then found in three generations of this family. It was not confined to one sex, and did not skip one generation to appear in the next. All the reported cases show the conditions to be a dominant characteristic and not sex bound, with the exception of three, the sporadic cases of Stahel (1936) and Zundel (1936), and the second case of Jonsson, Bostrom and Bringel. Undritz (1943) reexamined the films from the parents of Stahel's patient and found them both to be " partial carriers ", and the same was found with the father of Zundel's patient. Unfortunately the slide from the mother was not available. Nevertheless Undritz did not claim that the mode of inheritance in these two had been fully explained, and there still remains the case of Jonsson, Bostrom and Bringel, in which the blood of the parents was carefully examined and the possibility of their being " partial carriers " of the Pelger-Huet anomaly was excluded. Illegitimacy could provide the explanation in this instance. The blood groups are not given.

Schilling (1933) was the first to point out the possible medico-legal importance of the anomaly, and Undritz (1943) conjectured that as all the leucocytes are affected in this condition, the general body cells may be affected also, at least those which develop from the mesenchyme.

Tischendorf (1939) believes that the inheritance through the male line is rare, and females appear to have transmitted the condition more frequently than males.

Nachtsheim (1943) carried out a brilliant piece of research suggested by Undritz (1943) and has cleared up several of the problems connected with the inheritance of this anomaly of the leucocytes.

Nachtsheim stressed the view that all the cases of Pelger's anomaly reported must be heterozygote, as in no family were both parents carriers of the condition. By mating rabbits, both full carriers of the gene, Nachtsheim was successful in obtaining a few homozygous rabbits, but instead of the expected theoretical

numbers of 50% dominant heterozygotes, 25% recessive homozygotes and 25% dominant homozygotes, the number of dominant homozygotes was less than the theoretical number. He then found that many of these homozygote Pelger rabbits or "*Über Pelger*" died *in utero*, or shortly after birth. The surviving homozygotes, about 10%, were recognized by the following syndrome: arrested growth, severe malformations of the extremities especially in the fore limbs, scab formation around the mouth and nose, a constant flow of saliva, and emaciation.

The blood was examined by Undritz (1943), who found that all the leucocyte nuclei, neutrophile, eosinophile, basophile and monocyte, were round; even the lymphocytes and plasma cells showed extreme clumping of the nuclei. This observation removed any remaining doubt that the Pelger characteristic exists in eleven kinds of leucocytes without exception.

Nachtsheim succeeded in bringing one homozygote Pelger to sexual maturity and in breeding from it, by crossing it with a normal rabbit. The examination of the blood from the litter produced proved that the homozygous Pelger rabbit was indeed homozygous.

This important piece of research shows quite definitely that the Pelger anomaly can no longer be regarded as a "*Spiel der Natur*" as Schilling expresses it, or as a harmless blood picture. In double doses it may be lethal.

There has as yet been no description of the homozygous Pelger state in man; however, the possibility of such a condition as a rare cause of fœtal death should be borne in mind.

In the family here reported it appears that the gene will disappear with this generation. On the other hand the grandmother was always remarkably healthy and the mother had six children. Whether other factors are present, which together with the Pelger gene affect the individual to a greater degree, is a matter for future investigation.

Pelger (1928) and many of the earlier investigators, including Stahel (1937) believed the anomaly to be especially associated with tuberculosis, but further studies have not confirmed this. Stahel believed that the bearers of the anomaly have a deficient defence mechanism to deal with infection.

Direct functional tests of phagocytic activity were carried out by Leitner (1938) and the results showed that the mature Pelger leucocytes in the peripheral blood phagocytosed tubercle bacilli to the same extent as the leucocytes of a normal control; the immature cells, on the other hand, were less active.

With intercurrent acute disease the "shift to the left" may become very pronounced. In case four, reported by Jonsson (1948), in a patient admitted to hospital with the diagnosis of acute pneumonia, about one-third of the neutrophile leucocyte nuclei were round. At a later examination the changes due to the infection had disappeared and were replaced by the usual Pelger picture. In pus from furuncles, and in cantharides blisters, typical Pelger leucocytes have been observed (Hadorn and Blum, 1938).

Wegmann (1948) considers that the Pelger carrier has a constitutional weakness.

One of Zundel's (1935) patients showed a strong basophilic toxic granulation of the neutrophile cells without clinical cause, and two others responded to slight infections with a lymphatic reaction.

Undritz (1943) discusses in great detail the importance of the Pelger cells in comparative hæmatology, and believes that the differences between the varying nuclear morphology of the leucocytes of the mammals to the round nuclei of the leucocytes of the invertebrates, can now be explained. He considers that the polymorphonuclear cell with a round nucleus is phylogenetically the oldest, and that, with the development of the animal kingdom, the nuclei of polymorphonuclear cells have developed gradually from the round to the normal segmented type now seen in the higher mammals. The Pelger anomaly is therefore to be looked upon as a persistence of the phylogenetically oldest form of leucocyte.

SUMMARY

A family showing the Pelger-Huet anomaly of the leucocytes is reported.

The condition is discussed and its importance stressed.

The available literature has been reviewed.

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I have to thank Dr. Lorna Beveridge for help in reporting these cases. Dr. Beveridge sent me the patient Mrs. C., and when the condition was known, went to a great deal of trouble to obtain samples of the blood from other members of the family. It is also a pleasure to acknowledge the help received from The Royal Society of Medicine, from whom photostats of references unavailable in Australia were obtained.

REFERENCES

ALIEFF, M., and REEKERS, R. (1936), "*Weitere Falle der Pelgerschen Kernanomalie*", *Klin. Wchnschr.*, **15**, 1522.

BURGER, G. C. E. (1932), cited by Undritz (1937).

CHEVALLIER, P., and ELY, Z. (1936), "*Un cas d'anomalie de Pelger*", *Sang*, **10**, 398.

DEN HARTOG-JAGER, E. W. (1936), "*Pelger-Huetsche familiäre Kernanomalie bei einem Eingeborenen von Java*", *Med. Welt*, **10**, 993.

DIETZEL, K. (1925), "*Die Pelgersche familiäre Anomalie der Leucocyten unter Mitteilung der ersten in Deutschland beobachteten Familien*", Inauguration Dissertation, Erlangen, 25.

GRAMICCIA, G. (1951), cited in *Rev. hémat.*, **6**, 120.

HADORN, W., and BLUM, W. (1938), "*Ueber Pelger-Huetsche familiäre Kernanomalie der Leucocyten. Beschreibung einer weiteren Familie*", *Helvet. med. acta*, **5**, 93.

HUBER, W. (1939), "*Gleichzeitiges Vorkommen von Pelgerscher Varietät mit chronischer Myelose*", *Schweiz. med. Wchnschr.*, **20**, 556.

HUET, G. J. (1931), "*Over een familiare anomalie der leucocyten*", *Nederl. tijdschr. genees*, **73**, cited by van der Sar, *loc. cit.*

HUET, G. J. (1932), "*Ueber eine bisher unbekannte familiäre Anomalie der Leucocyten*", *Klin. Wchnschr.*, **11**, 1264.

JONSSON, E., BOSTROM, L., and BRINGEL, B. (1948), "Pelger-Huet's Anomaly of the Nuclei of the Leucocytes", *Acta med. Scandinav.*, **131**, 38.

JORDANS, G. H. W. (1932), cited by Undritz (1951).

KOKUBO, Y. (1936), "One Case of Pelger's Familial Nuclear Anomaly of Leucocytes (First Case Reported in Japan); Recommendation of Two Expressions Pseudo-myelocyte (Undritz) and Pseudo-metamyelocyte and Suggestion of Half Typical Pelger's Anomaly", *Tohoku J. Exper. Med.*, **29**, 519.

KOKUBO, Y. (1939), "The Second Family Case of Pelger's Familial Nuclear Anomaly of Leucocytes Reported in Japan and a Further Blood Investigation of Cases belonging to the First Family Case", *Tohoku J. Exper. Med.*, **36**, 1.

KNOLL, W., and SCHMIDT, G. (1939), "*Pelgerzellen im Säugetierblut*", *Folia haemat.*, **62**, 40.

LEITNER, ST. J. (1938), "*Weitere Untersuchungen über die Pelger-Huetsche familiäre Kernanomalie der Leucocyten*", *Folia haemat.*, **60**, 329.

LEITNER, ST. J. (1949), "Bone Marrow Biopsy", 305.

LEITNER, ST. J., and VAN LEEUWEN, J. J. (1935), "*Die Pelger-Huetsche familiäre Kernanomalie der Leucocyten*", *Klin. Wchnschr.*, **14**, 17.

LORENZ, E. (1937), "*Beitrag zur Kenntnis der Pelgerschen Kernanomalie*", Inaugural Dissertation, Berlin, 1937 ,cited by Arneth, *Folia haemat.*, **58**, 353.

LUDTMANN, H. (1937), "*Eine weitere deutsche Familie mit Pelgerscher Kernanomalie. Selbstbericht*", cited in *Schweiz. med. Wchnschr.*, **67**, 1932.

NACHTSHEIM, H. (1942), "*Die Pelger-Anomalie und ihre Vererbung bei Mensch und Tier*", *Erbarzt*, **10**, 175.

NACHTSHEIM, H. (1943), "*Die homozygoten Pelger und ihre Schicksal*", *ibidem*, **11**, 129.

NAEGELI, O. (1934), "*Probleme der heutigen Konstitutionslihre im Gebiete der inneren Medicin*", *Helvet. med. acta*, **1**, 104.

PETERSON, R. F. (1935), "Familial Shift to the Left of the Granular Leucocytes", *Am. J. Clin. Path.*, **5**, 249.

PELGER, K. (1928), "*Demonstratie van een paar zeldzaam voorkomende typenvan bloedlichaampjes en bespreking der patientin*", *Nederl. tijdschr. genees.*, **72**, 1178, cited by Nachtsheim.

PELGER, K. (1931), "*Demonstratie van praeparaten met eigenaardige, staafkernige neutrophiele cellen*", *Nederl. tijdschr. genees*, **73**, 439, cited by Van der Sar, *loc. cit.*

ROHR, K. (1949), "*Das menschliche Knochenmark*", 296.

ROOS, C. J. (1936), "*De familiare kernanomalie der leucocyten van Pelger en Huet*", *Nederl. tijdschr. genees*, **80**, 1906, cited by Nachtsheim, *loc. cit.*

SAR, VAN DER A. (1944), "The Pelger-Huet's Familial Nuclear Anomaly of the Leucocytes", *Am. J. Clin. Path.*, **14**, 544.

SCHILLING, V. (1933), "*Neue Fälle der Pelgerschen familiären Kernanomalie der Leucocyten*", *Deutsche med. Wchnschr.*, **59**, 724.

SCHILLING, V. (1936), "*Pelger-Huetsche familiäre Kernanomalie bei einem Eingeboren von Java*", *Med. Welt*, **10**, 994.

SCHMIDT, G. (1939), "*Ueber Pelger-Zellen im Blut von Säugetieren*", *Ztschr. f. mikr.-anat. Forsch.*, **46**, 459.

STAHEL, R. (1936), "*Ueber einen Fall von Pelgerscher konstitutioneller Zweikernigkeit der Neutrophilen ohne nachweisbaren Erbgang*", Dissertation, Zürich.

STAHEL, R. (1937), "*Neue Ansichten über Wesen und Bedeutung der Pelgerschen Varietät*", *Schweiz. med. Wchnschr.*, **67**, 308.

STODTMEISTER, R. (1936), "*Neuere Erhebungen zur Pelgerschen familiären Kernanomalie. II. Teil. Das Verhalten des Knochenmarkes bei der Pelgerschen familiären Kernanomalie*", *Deutsches Arch. f. klin. Med.*, **179**, 159.

TILESTON, W. (1937), "Familial Shift to the Left of the Leucocytes (Pelger's Nuclear Anomaly of the Leucocytes). With Report of a Case", *Ann. Int. Med.*, **11**, 675.

TISCHENDORF, W. (1939), "*Zwei weitere deutsche Familien mit Pelgerscher Kernanomalie*", *Folia haemat.*, **62**, 254.

UNDRITZ, E. (1933), "*Ueber das Vorkommen einer Familie im Wallis mit pseudoregenerativem weissem Blutbild, bedingt durch eine erbliche Kernform- und Kernstruktur-Varietät der Leukozyten*", *Schweiz. med. Wchnschr.*, **12**, 286.

UNDRITZ, E. (1937*a*), "*Die Pelgersche Varietät, nebst Mitteilung über eine bisher noch nicht beschriebene besondere Form (Teiträger)*", *Folia haemat.*, **56**, 416.

UNDRITZ, E. (1937*b*), "*Blut- und Knochenmarkuntersuchungen. 1. Neue Ergebnisse von Blut- und Knochenmarkuntersuchungen bei Vollträgern und dem Teilträger der Pelger-Huetschen Varietät.*", *Deutsche med Wchnschr.*, **63**, 1686.

UNDRITZ, E. (1939), "*Das Pelger-Huetsche Blutbild beim Tier und seine Bedeutung für die Entwicklungsgeschichte des Blutes*", *Schweiz. med. Wchnschr.*, **69**, 1177.

UNDRITZ, E. (1943), "*Das ausschliessliche Vorkommen reifer rundkerniger Leucocyten bei der reingezüchteten Pelger-Huetschen Anomalie des Kaninchens und die Bedeutung der Pelger-Leucocyten in der vergleichenden Hämatologie*", *Folia haemat.*, **67**, 249.

WEGMANN, T. (1948), "*Gehäuftes familiäres Vorkommen von Opticusatrophie und Pelgerscher Kernanomalie*", *Schweiz. med. Wchnschr.*, **78**, 996.

WEIGELDT, W. W. (1933), "*Familiäre Anomalie der Leucocyten (Pelgersche Kernanomalie)*", *München med. Wchnschr.*, **1**, 831.

ZUNDEL, W. (1935), "*Ein Fall von Pelgerscher familiärer Kernanomalie*", *Folia haemat.*, **54**, 1.

ZUNDEL, W. (1936), "*Neuere Erhebungen zur Pelgerschen familiären Kernanomalie. 1. Teil. Beobachtungen an zwei weiteren Familien mit Pelgerscher familiärer Kernanomalie*", *Deutsches Arch. f. klin. Med.*, **179**, 151.

THE RÔLE OF BLOOD COAGULATION IN THE PRODUCTION OF HÆMOLYSIS IN PAROXYSMAL NOCTURNAL HÆMOGLOBINURIA[1]

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HIJMANS VAN DEN BERGH (1911) reported a case of hæmolytic anæmia which has since been characterized as paroxysmal nocturnal hæmoglobinuria (P.N.H.) or the Marchiafava-Micheli syndrome. It is notable that Hijmans van den Bergh observed that the defect was of the red blood cell and that when serum, slightly acidified by carbon dioxide, was added to the cells *in vitro*, marked hæmolysis occurred.

The Ham (1939) acid hæmolysis test for P.N.H. may have been based upon these findings. Ham added several other criteria for diagnosis in addition to the acid hæmolysis test.

It was not until Crosby and Damashek (1950) and Crosby (1950) published their results that there was any suggestion that the coagulation of the blood was linked with the intravascular hæmolysis of P.N.H. However, it is well recognized that multiple thromboses are characteristic autopsy findings in patients dying of P.N.H. These authors suggested that serum accelerator globulin and thrombin were able to activate the hæmolytic factor in plasma or serum *in vitro* when liability to hæmolyse was determined by Ham's test. They also suggested that dicumarol might be of use in combating a hæmolytic crisis.

One patient with P.N.H. has been observed over a period of four years and he has shown frequent abnormalities in his blood coagulation system. The most noticeable of the *in vitro* findings was the marked hæmolysis which followed normal clotting of the patient's blood if it was incubated at 37° C. for fifteen to thirty minutes after clotting (pH 7·3). Although this phenomenon is listed by Ham among his criteria as frequent, but not necessarily general, it invariably occurred during the investigation of this patient.

The anti-coagulants heparin, citrate ions and oxalate ions prevented hæmolysis when they were present in concentrations sufficient to prevent clotting of the blood sample *in vitro*.

[1] This work was carried out under a grant from the National Health and Medical Research Council.

During the period of observation of this patient, Ham's test has been invariably given a positive response and all tests for hæmolysins negative results.

Because hæmolysis occurred after clotting between pH 7·3 and 7·45 it was thought desirable to investigate the relationship between clotting and hæmolysis within this pH range. Fewer artefacts should be introduced in this system than in one at pH 6·5 to 6·8.

It was found that when clotting occurred at pH 7·3 to 7·45 in the presence of the patient's cells, marked hæmolysis always occurred. When clotting did not occur, hæmolysis appeared only when the cells were mixed with serum acidified to pH 6·5 to 6·8 (Ham's test), The degree of hæmolysis was similar in both systems.

Some of the mixtures used to produce a clot, together with the controls, are set out in the accompanying table. To avoid unnecessary repetition, the results have been condensed. It is to be stressed that hæmolysis was never observed unless the patient's cells were used—cells from normal subjects never gave positive results.

Wherever a clot was formed in the presence of the patient's cells, gross hæmolysis occurred. The same results were obtained when fibrinogen and/or the thrombin used in the test were of human, bovine, canine or rabbit origin. When the fibrinogen content was maintained at the same level and the thrombin concentration progressively decreased, marked hæmolysis failed to occur only when clotting was completely inhibited.

The observation of Crosby and Damashek that fibrinolysin does not produce hæmolysis of P.N.H. cells *in vitro* was further substantiated by adding serum from a patient with severe fibrinolysis to the patient's cells (without acidification). No hæmolysis was observed during four hours.

The possible rôle of the intermediates in the thrombin-fibrinogen reaction in relation to hæmolysis in P.N.H. is subject to current investigation.

TABLE I

Patient's Cells.[1]	Other Reagents Added (pH 7·3).	Clot.	Hæmolysis.
0·1 ml.	0·6 ml. physiological saline	−	−
0·1 ml.	0·6 ml. bovine thrombin 20 units/ml.	−	−
0·1 ml.	0·6 ml. human thrombin 20 units/ml.	−	−
0·1 ml.	0·6 ml. oxalated plasma (human)	−	−
0·1 ml.	0·6 ml. oxalated plasma (canine)	−	−
0·1 ml.	0·6 ml. oxalated plasma (rabbit)	−	−
0·1 ml.	0·6 ml. fibrinogen (human)	−	−
0·1 ml.	0·6 ml. fibrinogen (canine)	−	−
0·1 ml.	0·1 ml. fibrinogen (rabbit)	−	−
0·1 ml.	0·3 ml. oxalated plasma (human, canine or rabbit) + 0·3 ml. thrombin (human, canine or rabbit)	+	+++
0·1 ml.	0·3 ml. fibrinogen (human, canine or rabbit) + 0·3 ml. thrombin (human, canine or rabbit)	+	+++
0·1 ml.	0·4 ml. serum (patient's chilled immediately) + 0·2 ml. thromboplastin after clotting)	−	−
0·1 ml.	0·2 ml. oxalated plasma (human) + 0·2 ml. M/40 $CaCl_2$ + 0·2 ml. thromboplastin)	+	+++
0·1 ml.	0·4 ml. serum + 0·2 ml. thrombin (bovine or human)	−	−
0·1 ml.	0·4 ml. oxalated plasma + 0·2 ml. thrombin (human or bovine)	+	+++

[1] The patient's cells were washed with physiological saline until the supernatant saline showed no obvious hæmolysis after centrifugation. The saline was pipetted off and the packed cell suspension was used. Packed cells from the patient's oxalated plasma usually occupied between 14% and 20% of the total volume of blood.

SUMMARY

One patient with paroxysmal nocturnal hæmoglobinuria has been investigated over a period of four years. His red blood cells have been found to undergo hæmolysis at normal blood pH when incubated for thirty minutes in any isotonic mixture which produces a fibrin clot.

The fibrinogen and thrombin used in any of these systems need not necessarily be human, but may be of bovine, canine or rabbit origin.

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Dr. C. R. B. Blackburn, Director of the Clinical Research Unit, Royal Prince Alfred Hospital, kindly allowed us to study a patient with paroxysmal nocturnal hæmoglobinuria. His cooperation and helpful suggestions during this work are greatly appreciated.

REFERENCES

CROSBY, W. H. (1950), "Paroxysmal Nocturnal Hemoglobinuria: A Specific Test for the Disease Based on the Ability of Thrombin to Activate the Hemolytic Factor", *Blood*, **5**, 843.

CROSBY, W. H., and DAMASHEK, W. (1950), "Paroxysmal Nocturnal Hemoglobunirua: The Mechanism of Hemolysis and its Relation to the Coagulation Mechanism", *Blood*, **5**, 822.

HAM, T. H. (1939), "Studies on Destruction of Red Blood Cells: Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria: An Investigation of the Mechanism of Hemolysis with Observations on Five Cases", *Arch. Int. Med.*, **64**, 1271.

HIJMANS, A. A. VAN DEN BERGH (1911), "*Ictère hémolitique avec crises hémoglobinuriques. Fragilité globulaire*", *Rev. méd.*, **31**, 63, quoted by Crosby and Damashek, *loc. cit.*

ANTIBODY TO THE ERYTHROCYTE-COATING POLYSACCHARIDE OF STAPHYLOCOCCI : ITS OCCURRENCE IN HUMAN SERA

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STUDIES of staphylococcal immunity in man have been concerned chiefly with antitoxic immunity. For example, there have been investigations of the serum levels of α antitoxin in various age groups (Bryce and Burnet, 1932), in various clinical infections (Dolman, 1935; Murray, 1935) and of the passage of antitoxin across the placenta to the fœtus (Murray, Calman and Lepine, 1950; Vahlquist, Lagercrantz and Nordbring, 1950). From numerous studies there has emerged little evidence that the presence of circulating antitoxin has any substantial effect on the course of staphylococcal infection in man and, as pointed out by Parrish (1951), this is particularly true in the case of newborn infants in whom, despite the presence of circulating antitoxin derived from the mother, infection with *Staph. pyogenes* often produces a fulminating disease differing markedly in clinical character from that in older children or adults. It has been considered likely by a number of workers (for example, Bøe, 1946) that a large element of hypersensitivity enters into the clinical picture produced by staphylococcal infection of the adult and older child, particularly in the skin lesions. At the same time, however, investigation of other antibodies especially of antibacterial ones, might afford further insight into the problems of staphylococcal immunity.

The description by Keogh and his co-workers (1948) of an erythrocyte-coating polysaccharide antigen in staphylococci suggested its use to measure antibody levels in human sera. While there is no direct evidence of any major rôle being played by this antibody in staphylococcal immunity, the antibody levels found in a wide range of normal human sera appear of sufficient interest to be reported.

PREPARATION OF THE ANTIGEN

The phenol insoluble erythrocyte-coating polysaccharide was prepared by the method of Warburton, Keogh and Williams (1949). The preparations were stored as a dry powder on watch glasses in a desiccator and dissolved in sterile physiological saline as 1 in 1000 solutions when required. These solutions were kept in the refrigerator when not in use, but it was found that inactivation occurred gradually under these conditions, the average period during which the antigen remained active being four to six weeks.

In preliminary studies, polysaccharide was prepared from a number of strains of coagulase positive staphylococci including Cowan's serological types I and III and strain 1339 (the propagating strain of Wilson and Atkinson's phage 3C) and from one strain of a coagulase negative *Staph. albus* isolated in the laboratory as a plate contaminant. The average yield of polysaccharide was 2·0 milligrammes per 0·4 grammes of cells (wet weight), which represented the 24 hours' growth on one Roux bottle of agar medium.

Serum from a rabbit immunized with strain 1339 was used to determine the antigen content of the various preparations. This serum had an antibody titre of 1 in 160, whatever the antigen used for its titration. The average antigen titres of preparations from the various strains were as follows: Cowan I, 1 in 256,000; Cowan III, 1 in 64,000; 1339, 1 in 128,000; and the *Staph. albus*, 1 in 16,000.

These results indicated that the phenol insoluble polysaccharide was a component common to both coagulase positive and negative staphylococci but that the amount of antigen extractable from the various strains used appeared to vary from strain to strain.

Antigen from strain 1339 was used in the human antibody titrations.

TITRATION OF SERUM ANTIBODY

The erythrocytes used were Group O human cells washed three times in saline before use. They were sensitized with 16 times the minimum amount of antigen found to render cells agglutinable by the 1339 rabbit serum. The sensitivity of the cells in each batch of titrations was checked by including a titration of the rabbit serum. Sera were inactivated at 56° C.

for twenty minutes before titration. The sera were titrated by the method of doubling dilutions, in a range from 1 in 2 to 1 in 256. To each tube which contained nine drops of diluted serum was added one drop of 5% sensitized erythrocytes and the tubes were well shaken. The degree of agglutination was read after the tubes had sedimented for one hour at room temperature. The antibody titre of the serum was taken as the reciprocal of that dilution showing complete agglutination of the cells, minor degrees of clumping being ignored.

SOURCES OF HUMAN SERA

The sera tested came from a number of sources. One series consisted of sera from normal women at parturition and the cord blood of their babies obtained at the same time. One series came from pregnant women attending an antenatal clinic. A series comparable in age came from non-pregnant women attending the Red Cross Blood Transfusion Service as blood donors. Sera from infants and children suffering from clinical conditions other than staphylococcal infections were obtained from the Royal Alexandra Hospital for Children. The remainder of the sera were taken at random from sera sent to this laboratory for application of the Wassermann test.

ANTIBODY TITRES IN HUMAN SERA

Sera from 553 individuals were examined and the results are set out in Table I. The sera have been divided into groups according to age and in the adults according to sex. The mean titre of each group is expressed in terms of the $\log_2$ mean and the standard deviation of each mean is given. It should be noted that there is, with one exception, considerable skewness in the distribution of the titres in each group.

In 26 of 32 infants at birth no antibody could be detected in serum from cord blood. In the remaining six infants small quantities of antibody were found, in one, identical with that of the mother, in the other five, considerably less than the mother's. Sera from the mothers of these infants had a mean titre of 4·12. Blood from 16 infants up to the age of four months likewise contained little or no antibody, the mean titre of 0·44 being comparable with that of 0·32 obtained from the newborn.

From the age of four months onwards, antibody was found in considerable quantities in individual sera. The mean titre in the age group 4 to 24 months was 2·55 and had risen to 3·75 in the 2 to 15 years age group.

The adult sera have been differentiated with regard to both age and sex, and, in the 15 to 40 female group, with regard to pregnancy.

TABLE I

Antibody Titres to the Erythrocyte-Coating Polysaccharide of the Staphylococcus in Human Sera

Serum Titre.		Children.				Adults.							
						15–40 Years.				41–60 Years.		61 Years. +	
Actual.	$\log_2$	At Birth.	0–4 Months.	4–24 Months.	2–15 Years.	Males.	Females.			Males.	Females.	Males.	Females.
							Non-Pregnant.	Pregnant.	At Delivery.				
<2	0	26	13	5	1	8	3			14	5	18	4
2	1	3	1	10	10	10	8	6	1	11	8	11	9
4	2	2		8	13	6	7	4	2	12	7	11	4
8	3	1	2	9	10	5	9	10	5	11	9	11	4
16	4			6	13	10	13	6	13	6	8	5	3
32	5			4	9	4	7	8	7	3	7	3	3
64	6			3	9	8	5	4	3		4	3	
128	7				3	1	1	9	1	3	2		
256	8				4		1	1		2		1	
Total number		32	16	45	72	52	54	48	32	62	50	63	27
$\log_2$ mean		0·31	0·44	2·56	3·75	2·92	3·35	4·22	4·12	2·32	3·08	2·02	2·07
S.D.		0·74	1·03	1·74	2·05	2·13	1·96		1·24	2·10	1·95	1·90	1·62

Examination of the data reveals certain differences and trends between these groups.

The first difference appears on examining the 15 to 40 female age group, and it concerns the influence of pregnancy on the antibody titres. The standard deviation for the females at delivery was lower than that of any other group among the adults, and this series of sera gave a normal distribution in contrast to the skewness shown by all other groups. The sera taken at delivery and at various stages during pregnancy have almost identical mean values (4·22 and 4·12) and are higher than those of any other groups of sera. In view of the difference in distribution of the "at delivery" group, calculations of statistical significance have been made only between the pregnant and non-pregnant females in this age group. The *t*-test gives $t_{100}=2\cdot26$, $0\cdot05>P>0\cdot02$, which is a significant difference.

Apart from the differences due to pregnancy, there is also a difference between the sexes to be observed in the age groups 15 to 40, 41 to 60, the difference disappearing after the age of 60. An analysis of variance in the age groups 15 to 40, 41 to 60 gives a value of $F=4\cdot69$, $P<0\cdot05$ between the sexes, which is a statistically significant difference in favour of the females. (The pregnant females have been omitted from these calculations since their higher values would have weighted the female values.)

In addition to the elimination of the sex difference with increasing age, there is also a downward trend with increasing age, the mean titres having fallen to 2·02 and 2·07 in the over 60 age group. Analysis of variance between the three age groups gives a value of $F=7\cdot37$, $P=0\cdot001$, which is highly significant.

Discussion

One point of particular interest in these results is the absence of antibody to the erythrocyte-coating polysaccharide of the staphylococcus in the majority of sera from the newborn and infants up to four months of age. It is apparent that, in general, this antibody does not pass across the placental barrier, even though it is present in large amounts in the maternal circulation. This absence of placental transmission is in marked contrast to the transmission of α antitoxin, the concentration of which may be even higher in the blood of the newborn than in that of their mothers (Murray, Calman and Lepine, 1950). Most antibacterial antibodies so far investigated have been found to be transmitted by the placenta, although the titres in the infants are not always as high as in the mothers. Exceptions to this are the agglutinins to *S. typhi* H (Schubert and Grünberg, 1949) and to the H and O antigens of a colon bacillus (see Vahlquist, Lagercrantz and Nordbring, 1950) which are not transmitted. The staphylococcal antibody must now be added to these exceptions.

It is tempting to postulate that it is the absence of this antibody from infants up to the age of four months that determines the differences between the clinical picture of staphylococcal infection in these young infants and that found in older children and adults. It should, however, be emphasized that so far there is no direct evidence that such is the case. What has been demonstrated is an immunological difference which parallels a clinical difference. In addition, the absence of antibody from these infants can be correlated with their susceptibility to nasal colonization by *Staph. pyogenes*. In a previous investigation (Rountree and Barbour, 1950) it was found that 48 of 54 infants born in hospital had become profuse nasal carriers of this organism at the age of seven days.

In this era of antibiotic therapy it is perhaps unfashionable to discuss the curative value of antisera, but the demonstration of the absence of antistaphylococcal antibody from young infants suggests that a trial should be made of the effect of adult pooled human serum on the progress of staphylococcal infection in these infants. Our results indicate that pooled adult sera should contain appreciable amounts of antibody and it might be worth while to use such sera in an attempt to confer a passive immunity on infants suffering from fulminating infections, combining their use with suitable antibiotic therapy. Furthermore, in view of the mounting incidence of antibiotic-resistant staphylococci in hospital environments, one may foresee many cases in the future in which antibiotic therapy will be valueless.

Apparently the presence of staphylococci in the noses or on the skins of young infants does not stimulate the production of the antibacterial antibody, since little or no antibody was found before the age of four months. High titres of the antibody were found in individual sera after this age and from the age of two years onwards most children had acquired a significant amount of circulating antibody. This is no doubt a reflection of the ubiquitous distribution of the staphylococci in the human environment.

In the adult sera, both sex and age differences of statistical significance are apparent. The fall in antibody titre with increasing age resembles that reported for other antibodies,

for example, the α antitoxin (Bryce and Burnet, 1932). The sex differences are perhaps of more interest, particularly their accentuation during pregnancy, and are suggestive of hormonal influences during the period of reproductive activity in the female.

SUMMARY

Antibody to the erythrocyte-coating polysaccharide of the staphylococcus has been measured in a series of human sera.

In general, the antibody is not transmitted from the mother to child, being seldom present in the newborn and in infants up to the age of four months. Its formation commences after the fourth month of life.

During the period of reproductive activity in the female, and in particular during pregnancy, higher amounts of antibody are found than in males of the same age group. The antibody level declines in old age.

ACKNOWLEDGEMENTS

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REFERENCES

BØE, J. (1946), "Importance of Bacterial Allergy in Relation to Cutaneous Infection with Staphylococci", *Acta dermat-venereol.*, **26**, 111.

BRYCE, L. M., and BURNET, F. M. (1932), "Natural Immunity to Staphylococcal Toxin", *J. Path. & Bact.*, **35**, 183.

BRYCE, L. M., and BURNET, F. M. (1932), "Natural Immunity to Staphylococcal Toxin", *J. Path. & Bact.*, **35**, 183.

DOLMAN, C. E. (1935), "Clinical Uses of Staphylococcus Toxoid", *Lancet*, **1**, 306.

KEOGH, E. V., NORTH, E. A., and WARBURTON, M. F. (1948), "Adsorption of Bacterial Polysaccharides to Erythrocytes", *Nature*, **161**, 687.

MURRAY, D. S. (1935), "Staphylococcus Toxoid: A Clinical Trial", *Lancet*, **1**, 303.

MURRAY, J., CALMAN, R. M., and LEPINE, A. (1950), "Transmission of Staphylococcal Antitoxin (Anti-hæmolysin) from Mother to Child", *Lancet*, **2**, 14.

PARRISH, H. J. (1951), "Inherited Immunity", *Brit. M. J.*, **1**, 1164.

ROUNTREE, P. M., and BARBOUR, R. G. H. (1950), "Staphylococcus Pyogenes in Newborn Babies in a Maternity Hospital", *M. J. Australia*, **1**, 525.

SCHUBERT, J., and GRÜNBERG, A. (1949), "*Zur Frage der Übertragung von immun-antikörpern von der Mutter auf das Kind.*", *Schweiz. med. Wchnschr.*, **79**, 1007.

VAHLQUIST, B., LAGERCRANTZ, R., and NORDBRING, F. (1950), "Maternal and Fœtal Titres of Antistreptolysin and Antistaphylolysin at Different Stages of Gestation", *Lancet*, **2**, 851.

WARBURTON, M. F., KEOGH, E. V., and WILLIAMS, S. W. (1949), "A Hæmagglutination Test for the Diagnosis of Influenzal Meningitis", *M. J. Australia*, **1**, 135.

HÆMORRHAGIC DISEASE DUE TO A CIRCULATING ANTICOAGULANT, WITH REPORT OF A CASE

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THE first case of hæmorrhagic disease due to an anticoagulant was reported by Lozner, Joliffe and Taylor in 1940. Since then about 20 similar cases have been reported, the only previous one from Australia being that of Fantl and Nance (1946).

The anticoagulants arise in two classes of patients: (i) those with known hæmophilia, occurring probably as a result of repeated blood transfusions, during which antibodies against the transfused "antihæmophiliac globulin" are formed; (ii) those who have not hæmophilia, but who develop signs and symptoms indistinguishable from hæmophilia. The pathogenesis of these cases is unknown.

A composite scheme of the present-day concept of blood coagulation is given below.

A. Slow phase:

(i) Thromboplastinogen (in serum or plasma? = antihæmophiliac globulin) + platelet factor = platelet enzyme = thromboplastinogenase → thromboplastin

(ii) Thromboplastin + calcium + prothrombin + factor V of Owren = accelerator substance of Fantl = plasma accelerator globulin of Saegers and Craddock = labile factor of Quick → thrombin

B. Rapid phase:

(i) Thrombin + factor V of Owren → factor VI of Owren = serum accelerator globulin of Ware = serum prothrombin conversion accelerator (SPCA) of Alexander

(ii) Prothrombin + factor VI of Owren → thrombin

(iii) Thrombin + fibrinogen → fibrin.

The synonyms of the various factors are given as well. There appear to be two phases: (i) a slow phase up to the liberation of thrombin, and (ii) a quick phase resulting in the more rapid formation of further thrombin by an auto-catalytic process, and the formation of fibrin.

REPORT OF A CASE

The patient whose history is given below had no personal or family history of bleeding until the age of forty-eight years, and the onset of the present illness. It seems impossible to accept him as a hæmophiliac. He had never had a blood transfusion until his hæmorrhagic disease started, and there was no reason for isoimmunization to occur. There appeared to be no precipitating cause for his illness that could be discovered *ante mortem* or *post mortem*. The history is as follows.

A male patient, aged forty-eight years, was admitted to the Professorial Unit of Medicine at the Brisbane Hospital on August 29, 1951. He had been perfectly well until six weeks before his admission, when he noticed vague ill health associated with aches and pains in the limbs, but no other symptoms. Three weeks before his admission to the unit he complained of pain in the right loin, followed the next day by frank hæmaturia. He was admitted to a country hospital for investigation. No abnormality was found other than slight anæmia and a coagulation time of twenty-eight minutes by the capillary tube method. After an injection of morphine into the left thigh, he developed a very large and painful hæmatoma of the thigh extending from the hip to the knee. He was transferred to the Brisbane Hospital for further study.

On examination of the patient, in addition to the hæmatoma of the leg he was found to have a fairly large, spontaneous, subcutaneous hæmatoma of the left side of the chest wall and left elbow region, and an effusion into the right superior tibio-fibular joint. His urine was obviously blood-stained, but the findings on physical examination were otherwise essentially normal. The tourniquet test for capillary fragility gave a negative result.

There was no personal or family history of hæmorrhagic tendency. The patient's father is alive and well at the age of seventy-seven years. His mother died of a " cancer ". He had two brothers and five sisters, and two children, all of whom are alive and well. He did not know the medical history of his grandparents, but had never heard of any " bleeders " in the family. He himself had never suffered from any bleeding tendency before. He had never had a blood transfusion until the present episode, and had not been taking any drugs.

It was at first thought that the patient was suffering from acute leuchæmia, but examination of the blood film did not support this. His blood count and the bleeding and coagulation times were as follows: On his admission to hospital, the erythrocytes numbered 3,000,000 per cubic millimetre and the hæmoglobin value was 58% (8·7 grammes *per centum*); the platelets numbered 300,000 per cubic millimetre. The leucocytes numbered 6,000 per cubic millimetre, 64% being neutrophile cells, 15% lymphocytes, 17% monocytes and 4% eosinophile cells. Examination of a blood film revealed no abnormality apart from a slight increase in the number of mononuclear cells. The bleeding time was two minutes and the coagulation time (capillary tube) was thirty-three minutes. By the Lee White method his coagulation time was shown to be about five hours, compared with a control of thirteen minutes. Addition of his blood to normal blood prolonged the coagulation time of the normal blood, and thereby showed the presence of an anticoagulant.

TABLE I.

Showing the Presence of an Anticoagulant.

Patient's Blood. (Millilitres.)	Blood of Control A. (Millilitres.)	Blood of Control B. (Millilitres.)	Coagulation Time. (Lee White Method.)
2·0	0·0	—	Over 4 hours.
1·6	0·4	—	60 minutes.
1·2	0·8	—	30 minutes.
0·8	1·2	—	18 minutes.
0·4	1·6	—	18 minutes.
0·0	2·0	—	11 minutes.
0·5	—	1·0	18 minutes.
1·5	—	1·0	Over 60 minutes.

It became obvious at this stage that an unusual condition had been encountered, and further investigations were carried out. Some of these gave the following results. (In particular the normal prothrombin time on several occasions should be noted.) The patient's blood was of group B, Rh-positive. His blood urea content was 63 milligrammes *per centum*. Attempts at culture and subculture from the blood were unsuccessful. The amount of ascorbic acid excreted in the urine was within the normal range. A second attempt at blood culture was unsuccessful. The serum bilirubin content was 0·3 milligramme *per centum*. The prothrombin time estimated by the Quick one-stage method was as follows: patient, 19·8 seconds; control 19·2 seconds. (A comparable result was obtained on several occasions.) No response was obtained to the Eagle Wassermann test, the Kahn standard test or the Kline diagnostic test. Electrophoresis of serum proteins by paper chromatography was carried out by Dr. Lederer, of the Queensland Institute of Medical Research, and a normal pattern was found. No anticoagulant was present then. The blood fibrinogen content was 170 milligrammes *per centum*.

Addition of protamine sulphate to the patient's blood on several occasions had no effect on the coagulation time. The anticoagulant was found to be present in the patient's plasma after it had been centrifuged at 3000 revolutions per minute for thirty minutes. Addition of the patient's blood to that of a known hæmophiliac with a normal coagulation time produced no anticoagulant effect. This test was repeated with a second hæmophiliac, but his coagulation time was three hours, and the results obtained were not significant.

TABLE II.

Effect on Hæmophiliac Blood.

Patient's Blood. (Millilitres.)	Hæmophiliac Blood. (Millilitres.)	Control Blood. (Millilitres.)	Coagulation Time. (Lee White Method.)
2·0	0·0	—	Over 6 hours.
1·5	0·5	—	35 minutes.
1·0[1]	1·0	—	10 minutes.
0·5	1·5	—	10 minutes.
0·0	2·0	—	10 minutes.
2·0	—	0·0	Over 6 hours.
1·5	—	0·5	120 minutes.
1·0	—	1·0	38 minutes.
0·5	—	1·5	16 minutes.
0·0	—	2·0	12 minutes.

[1] See addendum.

A prothrombin consumption test was performed. Unfortunately the anticoagulant was not demonstrable at that stage. However, the test showed that there was little consumption of prothrombin in twenty-four hours, compared with pronounced prothrombin consumption in a control in one hour. The test was subsequently repeated with similar results.

TABLE III.

Prothrombin Consumption Test, Quick One-Stage Method. (Anticoagulant not Demonstrable at this Stage.)

Time after Formation of a Solid Clot.	Prothrombin Time of Serum (Seconds).[1]					
	Tube (Control).			Tube (Patient).		
	1	2	3	1	2	3
15 minutes	11·0	—	—	12·0	—	—
30 minutes	40·0	27·0	—	12·4	12·0	—
45 minutes	58·6	41·0	40·0	12·0	12·0	12·4
60 minutes	62·0	50·2	44·2	11·8	11·0	11·8

[1] Prothrombin time twenty-four hours later, twenty-four seconds.

In an attempt to detect a possible antithromboplastin, the prothrombin time was determined with varying dilutions of thromboplastin.

The test was repeated, but anticoagulant was not demonstrable at this stage.

Soon after the patient's admission to hospital he had to be given a blood transfusion, because his hæmoglobin value fell to just over 4·5 grammes *per centum*. Next day he fell out of bed and suffered extensive bruising of the right side of his body, but fortunately did not strike his head. Subsequently he had to be given transfusions on many occasions because of a falling hæmoglobin value. Within three weeks of his admission to hospital he had lost his anticoagulant,

and it was thereafter impossible to demonstrate its presence, although his coagulation time remained persistently long.

TABLE IV.

Prothrombin Time Estimated by Varying Dilutions of Human Thromboplastin (Prepared According to Quick's Method).[1]

Dilutions of Thromboplastin.	Prothrombin Time. (Seconds.)	
	Control.	Patient.
Undiluted ..	15·0	15·0
1/200	30·5	41·0
1/500	38·6	55·0
1/800	45·4	71·4
1/1000	50·2	93·4
1/4000	59·8	113·0
1/8000	67·4	143·0

[1] Addition of a considerable excess of rabbit thromboplastin to plasma which had been standing, but unclotted, for about thirty minutes, caused almost immediate clotting.

TABLE V.

The Test Recorded in Table IV Repeated. (Anticoagulant not Demonstrable at this Stage.)

Dilutions of Thromboplastin.	Prothrombin Time (Seconds).		
	Control A.	Control B.	Patient.
Undiluted ..	18·2	17·6	17·8
1/200	31·4	32·6	30·0
1/500	42·0	42·6	37·0
1/800	55·0	54·2	50·4
1/1000 ..	57·0	57·4	60·0
1/4000 ..	105·0	95·0	75·0

From this point on his "laboratory behaviour" was that of a hæmophiliac, although his clinical course was not. The coagulation times were persistently prolonged, as is shown in Table VI. However, the

TABLE VI.

Coagulation Times.

Date.	Coagulation Time.
Approximately 28. 8.51	28 minutes (capillary tube method).
30. 8.51	33 minutes (capillary tube method).
3. 9.51	5 hours (Lee White method).
11. 9.51	6 hours (Lee White method).
21. 9.51	15 minutes (Lee White method).
26. 9.51	50 minutes (Lee White method).
15.10.51	30 minutes (Lee White method).
23.10.51	25 minutes (Lee White method).

addition of normal blood to the patient's blood reduced the coagulation time to normal on many occasions. A typical example is shown in Table VII. The prothrombin consumption test still gave a result of hæmophiliac type.

Three weeks after his admission to hospital the patient developed an enormous spontaneous hæmatoma in the tissues of the back and the left shoulder. This was exceedingly painful, and lasted for many weeks. His coagulation time the morning after this was fifteen minutes, the lowest it had ever been.

In contradistinction to the effect in hæmophilia, blood transfusion had no effect in stopping the bleeding in this or any other hæmorrhagic episode.

Six weeks elapsed before the next hæmorrhage occurred, and during that time the patient made a good clinical recovery despite occasional blood transfusions for a falling hæmoglobin value. During this time all attempts to demonstrate an anticoagulant in appreciable quantities were futile—addition of normal blood in the test tube always produced a normal coagulation time.

TABLE VII.

Patient's Blood. (Millilitres.)	Control's Blood. (Millilitres.)	Coagulation Time, Lee White Method. (Seconds.)
2·0	0·0	40 minutes.
2·0	0·0	35 minutes.
1·5	0·5	7 minutes.
1·0	1·0	7 minutes.
0·5	1·5	7 minutes.
0·0	2·0	7 minutes.
0·0	2·0	7 minutes.

On November 7 he developed a large hæmatoma on the left arm, again without any cause. The end came on November 14, when he developed a hæmatoma in the floor of his mouth. This increased slowly over a period of about twenty-four hours, and finally caused complete respiratory obstruction. The patient was given continuous transfusions over this period, and in fact had received a litre of blood on the day before the obstruction occurred. An attempt was made to evacuate the hæmatoma through the floor of the mouth, but the blood was diffusely distributed throughout the tissues and could not be removed. When obstruction became complete, a tracheotomy was performed at the bedside and respiration was reestablished for some hours, but the patient then died.

On the basis of the scheme already given, some attempt may be made to find the site of action of the anticoagulant. (i) The calcium level never falls sufficiently to affect the clotting mechanism in life, so a deficiency here can be ruled out. (ii) The presence of a heparin-like substance is ruled out because of the failure of protamine sulphate to affect the coagulation time. (iii) The fibrinogen level, although rather low, was not sufficiently reduced to affect the coagulation time, nor would a deficiency act as an anticoagulant. (iv) The normal prothrombin times almost certainly rule out a deficiency of prothrombin or of factor V. (v) The platelets were normal in number, and a deficiency would act as an inhibitor of coagulation time, but not as an anticoagulant. (vi) The clot when produced appeared to be normal, clot retraction occurred normally, and there was no evidence of fibrinolysis of a formed clot. (vii) A deficiency of factor VI alone would not act as an anticoagulant. (viii) The addition of a considerable excess of thromboplastin rapidly produced a normal clot,

so presumably the amount of thrombin formed was normal. (ix) This leaves a deficiency of thromboplastin or one of its precursors, caused by the presence of a substance acting against it. Since the patient was not a hæmophiliac, there seems no reason to suppose a deficiency of antihæmophiliac globulin. The fact that the patient's blood had no anticoagulant effect against hæmophiliac blood suggests that the anticoagulant may have been directed against this globulin. The lengthening of the prothrombin time with increasing dilutions of thromboplastin suggests that the anticoagulant may have been an antithromboplastin, this being overcome by the addition of a considerable excess of thromboplastin.

It was not possible to go past this stage. There were many further investigations which it was hoped would be carried out, but they could not be performed, because after about three weeks the anticoagulant could no longer be demonstrated. Why in subsequent laboratory investigations the patient behaved as an apparent hæmophiliac is not known. Certainly his clinical picture, particularly his failure to respond to blood transfusion, was not that of hæmophilia. Possibly the anticoagulant was present in small quantities, which were sufficient to prolong the patient's coagulation time, but were overcome by the addition of small quantities of normal blood, which usually contains an excess of all essentials to normal clotting.

ACKNOWLEDGEMENTS

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REFERENCES

FANTL, P., and NANCE, M. H. (1946), " An Acquired Hæmorrhagic Disease in a Female due to an Inhibitor of Blood Coagulation ", *M. J. Australia*, **2**, 125.

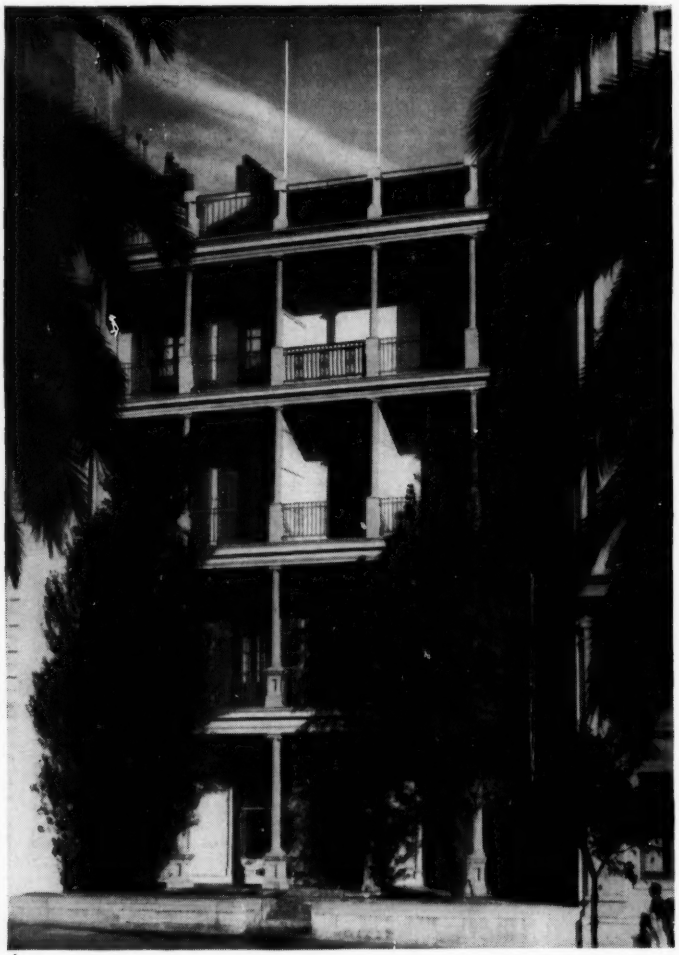
LOZNER, E. L., JOLIFFE, L. S., and TAYLOR, F. H. L. (1940), " Hæmorrhagic Diathesis with a Prolonged Coagulation Time, Associated with a Circulating Anticoagulant ", *Am. J. M. Sc.*, **199**, 318.

ADDENDUM

All investigations were carried out in glass tubes at room temperature with normal controls. Silicone coated tubes were not easily available. No antihæmophiliac globulin was available. The hæmophiliac whose blood had a coagulation time of ten minutes has a well authenticated family and personal history of hæmophilia. It is difficult to account for the third entry in the first column of Table II, but it is included for the sake of completeness, as it represents what happened.

The Royal Australasian College of Physicians

TWENTY-ONE years ago a small band of physicians met in Melbourne to found, under the presidency of Sir Richard Stawell, The Association of Physicians of Australia. The object of this body was to promote and maintain, through personal friendship and mutual interchange of knowledge and ideas, the high ethical and professional standards of practising physicians. Membership was originally limited to fifty persons who were teachers of clinical medicine and physicians of high professional attainment, but it soon became evident that the privileges and benefits of the Association should be shared more widely. To this end it was decided that the Association should found a College of Physicians along the lines of similar institutions in Great Britain and elsewhere.



Encouraged by the good wishes of other Colleges throughout the English-speaking world,

the first Council, with Sir Charles Bickerton Blackburn as President, and the Foundation Fellows undertook the responsibility of establishing the new College and on April 1, 1938, The Royal Australasian College of Physicians was legally incorporated. The ceremony of inauguration was held with fitting ritual in the Great Hall of The University of Sydney on December 14, 1938. Sydney was chosen for the headquarters of the College and here, in a building of early colonial architecture, an appropriate home was formally opened in September 1939. The darkening shadow of war fell on this celebration but during the following years the College continued its activities, enlarging its Membership and maintaining the standards of medical scholarship.

The essential aims of the College are to promote a scientific approach to the problems of disease, to bring physicians together for their common benefit, to enhance their service to the nation and to promote medical research. These aims are achieved not only by the holding of general meetings and examinations in Australia and New Zealand, but also by professional and social activities in the Dominion and the individual States which keep the flames of friendship and learning aglow in each centre; by the encouragement of post-graduate study, in particular through personal contact with distinguished teachers from overseas; by the provision of scholarships; and by long-range plans for medical research. The generosity of public-spirited men and of Fellows and Members has made research a practical and valuable project of the College. The alliance of clinical medicine with the advance of science requires a dissemination of both the spoken and written word, and while its debates on medical questions are the modern counterpart of the teaching of the peripatetic philosophers of ancient culture, the responsibility of the College is the greater as it sets forth its work and its views in print.

The Membership examination, with its strict requirements of learning and clinical skill demanded by the first Censor-in-Chief, S. O. Cowen, and his colleagues and successors, has already had a salutary influence on Australasian medicine. In this respect and in others relating to professional standards, the Dominion branch of the College in New Zealand has played an active and important part. Following the example of the Royal College of Physicians of London, the Fellowship is granted to distinguished physicians and senior Members after election by the General Body of Fellows.

At the beginning of 1952, 289 Fellows and 358 Members made up the ranks of the College. Of these, 230 Fellows and 295 Members were resident in Australia, 52 Fellows and 59 Members in New Zealand, and 7 Fellows and 4 Members in countries overseas.

The office of President has been held in succession by Sir Charles Bickerton Blackburn, of Sydney, 1938–1940; Sir Sidney Sewell (deceased), of Melbourne, 1940–1942; Sir Trent Champion de Crespigny, of Adelaide, 1942–1944; Harold Ritchie, of Sydney, 1944–1946; S. A. Smith, of Sydney, 1946–1948; L. S. Latham (deceased), of Melbourne, 1948–1950; and A. W. Holmes à Court, of Sydney, 1950–1952.

The College holds an annual meeting and an ordinary meeting in each year. Most of these have taken place in Sydney and Melbourne, but others have been held in Auckland, Brisbane, Adelaide and Perth. A report of the ordinary meeting held in Perth in October 1951 is given in the following pages.

Proceedings of The Royal Australasian College of Physicians

ORDINARY MEETING, 1951

An Ordinary Meeting of the College was held in Perth on October 16, 17, 18 and 19, 1951. It was attended by 42 Fellows and Members representing all States of the Commonwealth. The vast distance of New Zealand from Perth prevented the attendance of members of the College from the Dominion.

Scientific Sessions

Cyril Fortune (Perth) opened the first Scientific Session with a paper entitled " Vascular Abnormalities in the Lung " (page 42).

A. J. M. Dobson (Hobart) discussed " Prognosis in Chronic Nephritis ", basing his views on 80 cases of nephritis studied in detail at the Royal Hobart Hospital during the previous six years. As it was possible to classify only 50 of these cases, Dr. Dobson emphasized the need for gauging prognosis in the light of a review of factors in the individual case rather than its determination on the basis of a given type. He called attention to the significance of the association of formed elements in the urine with albuminuria. Albuminuric retinopathy was compatible with a longer period of life for patients than the usual two years begrudged to them as was proved by two patients who survived five years after this sign had been first recognized. The value of tests of renal function was discussed at some length and the need for an over-all review of a series of the same or different tests was emphasized. The ability of the kidneys to secrete a urine of a specific gravity of 1020 or more was no excuse for the abandonment of all other tests of renal function. The speaker maintained that the nature of the anæmia of chronic nephritis bore some relation to the prognosis and he adduced evidence to show that in most instances it was a hyperplastic anæmia associated with a maturation arrest at the prenormoblast or the normoblast stage. The paper was illustrated by colour photomicrographs of kidney sections, blood films and bone marrow biopsies.

A. J. Barnett (Melbourne) delivered an address entitled " The Rôle of the Sympathetic Nervous System in Essential Hypertension ". Discussing the mechanism by which the normal blood pressure was maintained, he called attention to the importance of the control of tonus in the peripheral arterioles. After discussing the influence of the sympathetic nervous system and of endocrine and other humoral factors, and an intrinsic property of the vessel wall as possible agents in the control of vessel tonus, he came to the conclusion that the present evidence was insufficient to accept any one of them as the cause of the maintenance of tone. He assumed that the blood pressure in essential hypertension was also the result of increased vascular tone, though the possibility of increased cardiac action could not be entirely excluded. The effect of sedation and the cold pressor test on hypertension, and the therapeutic response to lumbo-dorsal sympathectomy and ganglion-blocking agents, suggested that the sympathetic nervous system played some part at least in the arteriolar hypertonus. At the same time the experiments of Selye, who induced hypertension by means of suprarenal substances, suggested that these too might play a part. Finally the experiments of Goldenberg who demonstrated a greater vascular response to noradrenaline by hypertensive subjects than that shown by normal persons, suggested that there was an increased irritability inherent in the hypertensive arteriole. Integrating these observations, Dr. Barnett proposed an hypothesis that as a result of such factors as heredity or suprarenal activity, the vessels of the hypertensive patient are abnormally responsive to the normal level of sympathetic activity or of circulating epinephrine.

Ruthven Blackburn (Sydney), for the Clinical Research Unit of the Royal Prince Alfred Hospital, gave " A Preliminary Report on the Experimental Production of ' Lower Nephron Nephrosis ' ". Controlled intravascular hæmolysis had been induced in human beings by the infusion of distilled water into peripheral veins. Observations had been made on the changes in glomerular filtration rate (measured as inulin clearance), effective renal plasma flow (measured as low concentration " Diodrast " clearance), and urine flow in relationship to plasma and urine hæmoglobin concentrations. Marked oliguria had occurred, urine flow being reduced to less than 1% of the control values. At the same time the apparent renal plasma flow had decreased considerably and, to a lesser extent, the apparent glomerular filtration rate. The systemic blood pressure, pulse rate, and temperature had been unchanged. These results had been interpreted as indicating the existence of constriction of the renal arterioles, efferent rather than afferent, and disturbance of tubular function. The changes were similar to those observed in " lower nephron nephrosis " following incompatible blood transfusion. Determination of extraction ratios of inulin and " Diodrast " together and further investigations of the renal effects of intravascular hæmolysis are in progress.

J. L. Frew (Melbourne) delivered a paper entitled " Renal Biopsy in Hypertension " and Gerald Moss (Perth) discussed " Cerebral Angiomatous Malformations ".

Clinical Meeting

A clinical meeting was arranged at the Royal Perth Hospital by Bruce Hunt and John Phillips.

College Ceremony

A Ceremony was held in the Winthrop Hall of the University of Western Australia in the presence of the State Administrator, Sir John Dwyer. The audience of 500 guests included Fellows and Members and their wives, representatives of the Government of Western Australia and many prominent citizens of Perth.

The President (A. W. Holmes à Court) welcomed the visitors and delivered a short address. He said this was the first meeting of the College to be held in Perth. He reviewed the history of the establishment of the College and indicated the purposes for which it was founded, namely, the promotion of a scientific attitude

to the problems of disease, the maintenance of the highest professional standards and the development of medical research.

The guest speaker was Professor Frederick Alexander, Professor of Modern History in the University of Western Australia, who gave an address entitled "Australia's Rôle in the Contemporary Commonwealth" (*The Medical Journal of Australia*, January 5, 1952, page 1). Guests were entertained at supper in the Union Refectory.

COUNCIL MEETING

The Council met in the Senate Room of the University of Western Australia on October 16 and 17, 1951. At the invitation of the President there were also present the Chairman and the Honorary Secretary of the Western Australian State Committee, Gordon Hislop and Kendall Pawsey respectively.

Election of Office-Bearers, 1952–1954. The following were elected by the Council to take office in May 1952:

President: Alex P. Murphy

Vice-Presidents: J. G. Hayden, Guy Lendon, I. McD. Allen

Censor-in-Chief: C. G. McDonald

Honorary Treasurer: W. P. MacCallum

Honorary Secretary: H. Maynard Rennie.

Incidence of Coronary Disease in Western Australia. The question of the growth in the incidence of coronary disease in Western Australia had been raised in a letter from the Commissioner of Public Health in that State in which he invited suggestions from the College regarding the causes of the increase and any remedial measures which might be adopted to combat it. A survey of death certificates had led to the view that there was a mounting incidence of coronary disease in Western Australia. Reports prepared by the Department of Health in Western Australia had been forwarded to the College, which had appointed a sub-committee to investigate the matter. The members of the sub-committee, with the assistance of the Consulting Statistician to the National Health and Medical Research Council, Dr. H. O. Lancaster, had investigated the whole question and their report was now before the Council. In the discussion the opinion was expressed that views on the subject were so conflicting and so many factors were involved in the whole question of coronary disease that the College should not at the present time attempt to give any clear opinion of the questions raised.

Publication of "Australasian Annals of Medicine". It was decided to proceed with the publication of a journal of internal medicine and the allied sciences which would incorporate and replace the "Proceedings of The Royal Australasian College of Physicians". An arrangement was therefore entered into with the Australasian Medical Publishing Company, Limited, whereby a journal under the title of AUSTRALASIAN ANNALS OF MEDICINE should be published for the College twice yearly in the months of May and November, the first issue to appear in May 1952.

Admission of Members. The following were admitted to Membership of the College in October 1951: B. T. Dowd, H. M. Landecker, A. A. Young, of New South Wales; R. T. J. Galbally, T. H. Hurley, A. W. Venables, of Victoria; R. B. Lefroy, of Western Australia; A. E. Erenstrom, C. H. Garlick, T. H. Pullar, of New Zealand.

Travelling Scholarship. An anonymous foundation to provide for a travelling scholarship was gratefully accepted by the Council. The purpose of the scholarship is to improve scientific knowledge and teaching in Australia and New Zealand. The scholarship, which has a value of £1,200 Australian currency, may be awarded each year for a period of five years to a Fellow or Member of the College. Each scholar will be asked to give an undertaking to return to Australasia to carry out the purposes of the foundation.

Increased Representation of New Zealand on the Council. The Council resolved to submit to a general meeting a recommendation that the Articles of Association be amended to provide an increased representation from the Dominion of New Zealand upon the Council. It is proposed that the Dominion shall in future be represented by two elected Councillors in addition to a Vice-President.

Control of Cortisone in Australia. At the request of the Department of Health and the Department of Trade and Customs the College has cooperated in the control and allocation of supplies of cortisone throughout Australia.

Research Activities. The Council adopted the report of the Research Advisory Committee. This included reference to the work on hypertension being carried out at St. Vincent's Hospital, Sydney, by F. B. Byrom. A grant in aid had been made to Dr. Byrom by the College. Other grants are available to approved applicants engaged in either full-time or part-time research.

GENERAL

Obituary. The Council reports with regret the death of Dr. F. S. Hone of South Australia, and Dr. Frank Fitchett of New Zealand, who were Fellows of the College; and of Dr. S. G. Bradfield of New South Wales and Dr. Martin Alexander of England, who were Members of the College.

Honours. The Council records its pleasure at the awards of honours to the following Fellows of the College: Sir Samuel Burston, K.B.E., Air Commodore E. A. Daley, C.B.E., and Surgeon-Captain D. A. Pritchard, C.B.E.

Scholarships. The Wunderly Travelling Scholarships in Thoracic Disease were awarded for 1952 to A. H. Campbell of Victoria and G. L. Brinkman of New Zealand.

The Joseph Thornton Tweddle Research Scholarship for 1951 was awarded to A. W. Steinbeck.

The Margaret Ryan Scholarship in Medicine at St. Vincent's Hospital, Melbourne, for 1951 was awarded to M. A. Griffin and the T. F. Ryan Scholarship in Medicine at The Royal Melbourne Hospital for 1951 was awarded to R. H. Stanistreet.

Research Fund. Donations to the Research Fund of the College, which now totals £58,775 1s. 6d., have been received from:

	£	s.	d.
Mr. Adolph Basser	50,000	0	0
Mr. E. J. Hallstrom	2,500	0	0
Mr. Oscar O'Brien	1,000	0	0
Washington H. Soul, Pattinson and Company Limited	1,000	0	0
Mr. Martin McIlrath	500	0	0
Sir Mark and Lady Sheldon	500	0	0
Timber Trade Mutual Insurance Limited	500	0	0
F. W. Hughes Proprietary Limited	250	0	0
Mutual Life and Citizens' Assurance Company Limited	250	0	0
Sydney Snow Proprietary Limited	250	0	0
Commercial Banking Company of Sydney Limited	250	0	0
Austral Motors Proprietary Ltd.	200	0	0
Mr. and Mrs. P. L. Gowing and Gowing Bros. Ltd.	200	0	0
Manufacturers' Mutual Insurance Limited	157	10	0
Mr. K. C. K. Dalton	100	0	0
David Jones Limited	100	0	0
Robert Nettlefold Proprietary Limited	100	0	0
Westcott, Hazell and Company Limited	100	0	0
Cascade Brewery Company Limited	100	0	0
Mark Foy's Limited	100	0	0
Mr. Frank Economus	52	10	0
John Sands Proprietary Limited	52	10	0
Hazell and Moore Proprietary Limited	52	10	0
J. J. Sullivan and Company	50	0	0
Mrs. V. M. Macansh	50	0	0
Farmer and Company Limited	50	0	0
Taylors Elliotts Proprietary Limited	26	5	0
Mr. F. J. Wallis	25	0	0
Tractors, Diesels and Equipment Proprietary Limited	25	0	0
D. Maclean Proprietary Limited	20	0	0
Mr. H. M. Murray	10	0	0
Fellows and Members	203	16	6
	£58,775	1	6

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